



New Methodology for the Medium Scale Solid-Phase Synthesis of Small Drug Molecules

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Synthesis and scale up of small molecules on solid phase - the use of Versabeads™

PhD – dissertation

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H. Lundbeck A/S,
VersaMatrix A/S
and
Technical University of Denmark

2006

“A school should be the most beautiful place in every town and village –
so beautiful that the punishment for undutiful children should be
that they are debarred from going to school the following day.”

Oscar Wilde

*Dedicated with love and respect to my parents – without whom I would not be here
And to all my friends, who make it worthwhile to be here*

Abstract

The aim of this dissertation was to investigate the possibility of synthesising small nitrogen heterocycles using solid-phase techniques, exploiting the properties of the novel, hydrophilic solid phase Versabeads.

Chapter 1 contains a general introduction to solid-phase chemistry and describes how Process Chemistry has the potential to benefit from the employment of solid-phase techniques in the initial scale-up of a drug candidate. The scope and problems concerning the use of solid-phase chemistry on a larger scale in the synthesis of small organic molecules are discussed.

Chapter 2 is a description of the development of the synthesis and use of two known solid-phase linkers: the REM linker and the carbamate linker, as well as the use of these two linkers in syntheses of piperazine derivatives.

The development of a gram-scale synthesis protocol of a series of *N*-aryl and *N*-aryl-*N'*-methyl piperazines based on the immobilization of bis(chloroethyl)amine on resin through the carbamate linker is described in Chapter 3. The scale-up to 0.19 mol reaction scale of a synthesis of an aryl piperazine on resin is demonstrated, as well as the possibility for reuse of the resin.

During the work on the piperazine-forming reaction an interesting side reaction was discovered, which formed a previously unknown imidazolidin-2-one through cyclative cleavage. The investigations into the scope and mechanism of this reaction are reported in chapter 4.

Chapter 5 concerns the use of the solid phase as a support for *meso*-tetraphenylmetalloporphyrins, a well-known class of catalysts in organic chemistry. Two different *meso*-tetraphenylporphyrins were successfully immobilized on the resin and metallated with manganese. When tested as catalysts in the aqueous oxidation of sulphur, good conversions were obtained but the catalytic complexes appear to be cleaved from the resin under the reaction conditions. Attempts to synthesise porphyrins directly on the resin proved unsuccessful.

Dansk resume

Det arbejde der beskrives i denne afhandling havde til formål at undersøge mulighederne for at syntetisere små nitrogenheterocycler ved hjælp af fastfase kemi på den nye, hydrofile resin Versabeads.

Kapitel 1 giver en generel introduktion til fastfasekemi og beskriver hvordan Proceskemi muligvis kan udnytte denne teknik til den indledende opskalering af syntesen af nye lægemiddelkandidater.

Kapitel 2 beskriver arbejdet med at udvikle fastfasesyntese baseret på to kendte linker-strukturer: REM linkeren og carbamat – linkeren. De to linkere bliver testet i syntesen af et antal piperazin-derivater.

Kapitel 3 omhandler udviklingen af en synteseprotokol til syntese af en serie *N*-aryl og *N*-aryl-*N'*-methylpiperaziner, baseret på bis(chlorethyl)amin immobiliseret på resinen gennem carbamatlinkeren. En af disse synteser bliver opskaleret til 0.19 mol skala. Desuden bliver mulighederne for at genbruge resinen undersøgt.

Under arbejdet med at udvikle piperazinsyntesen viste der sig en interessant sidereaktion. Der blev dannet en hidtil ukendt imidazolidin-2-on forbindelse ved cyklativ kløvning fra resinen. Mekanismen bag denne reaktion bliver undersøgt nærmere i kapitel 4.

I kapitel 5 undersøges resinens egenskaber som fast fase bærer af *meso*-tetraphenyl metalloporphyriner, der er kendte komplekser med katalytisk aktivitet. To forskellige *meso*- tetraphenylporphyriner bliver bundet kovalent til resinen og kompleksbundet med mangan. De herved dannede katalytiske komplekser er effektive katalysatorer for oxidation af sulfider, men synes at kløves fra resinen under reaktionsbetingelserne. Forsøg på porphyrinsyntese direkte på resinen viste sig ikke at give resultat.

Preface

The present PhD dissertation summarizes work carried out in connection with my enrolment as a PhD student at the Department of Chemistry at the Technical University of Denmark from March 2003 to February 2006. The PhD was financed under the Danish Industrial PhD Fellowship in cooperation between the Danish Ministry of Science, Technology and Development and the companies H. Lundbeck A/S and VersaMatrix A/S.

Dr. Robert Dancer of H. Lundbeck A/S and Prof. David Tanner from the Technical University of Denmark supervised the PhD work. Dr. Michael Sommer, Dr. Ole Nielsen and Dr Thomas Ruhland of H. Lundbeck A/S Dr. Ib Johannsen of VersaMatrix A/S were joint members of the supervisor group and have contributed with invaluable input, information and advice.

The main topic of the present work was to investigate the possibilities for gram-scale synthesis of small molecules (molar weight < 500 g/mol) through the use of Versabeads, a resin developed by Versamatrix A/S. This work is covered in the first part of the thesis leading to gram-scale synthesis of piperazines on-resin. Parts of this work have been publicized previously as an article in *Synthesis*.

During the course of the work with the piperazines an interesting side reaction, which formed a previously unknown imidazolidin-2-one was discovered. The scope and mechanism of this reaction is investigated in the second part of the thesis.

From April to September 2004 I had the honour and pleasure of working in the group of Prof. Steven V. Ley at the Department of Chemistry, University of Cambridge (UK). My work in the Ley Group consisted in an investigation of the possibility of using Versabeads as a solid support for immobilization of a catalytic complex based on *meso*-tetraphenyl manganese porphyrin. The work done at the Ley group is described in the last part of the thesis.

I would like to thank my supervisors for all their help and support over the years. Special thanks to Dr. Dancer for taking me as student and giving me excellent supervision in all aspects of the project and for becoming such a good acquaintance.

I would also like to thank all my colleagues and co-workers at H. Lundbeck A/S and Versamatrix A/S for their help and support during the three years. A special thanks goes to Dr. Jens Chr. Madsen from the Compound ID and Purification Department for setting up the NMR experiments for the gel-phase NMR, and to Flemming Rasmussen for being such a good labmate.

A very special thanks goes to Professor Ley for allowing me to come and work six instructive months in the Ley group, to Dr Ian Baxendale and Dr. Jason Siu for supervision during this stay, to Dr. Peter Grice for NMR and to all the people at the Whiffen lab for making it such a fantastic experience to work there. A thanks also goes to Dr. Steve Boreham and Chris Rolfe from the Department of Geography at the University of Cambridge for help in performing the Atomic Absorption Spectroscopy of the catalytic complexes.

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Abbreviations

Ac = acetyl
AAS = Atomic Absorption Spectroscopy
Ar = Aryl
ATR = Attenuated Total Reflection
BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
boc = *tert*-butoxycarbonyl
dba = dibenzylacetone
DBU = 1,8- diazabicyclo[5,4,0]undec-7-ene
DCM = dichloromethane
DIC = *N,N*-diisopropylcarbodiimide
DIPEA = diisopropyl ethylamine
DMA = dimethylacetamide
DME = diethylene glycol dimethyl ether
DMF = dimethyl formamide
dppf = 1,1'-bis(diphenylphosphino)ferrocene
ELSD = Electronic Light Scattering Detection
Et = ethyl
Fmoc = 9-Fluorenylmethoxycarbonyl
FTIR = Fourier Transformed Infra Red
GC = gas chromatography
HOBt = 1-hydroxybenzotriazole
HPLC = high pressure liquid chromatography
iPr = isopropyl
LC/MS = Liquid Chromatography/Mass Spectrofotometry
MAS = Magic Angle Spinning
Me = methyl
MeCN = acetonitrile
Mes = 2,4,6 – trimethylphenyl
MIBK = Methyl isobutyl ketone
Ms = methanesulfonyl
MODDE =
nBu = n-butyl
nPr = n-propyl
NIR = Near Infrared Spectroscopy
NMP = *N*-methylpyrrolidone
NMR = Nuclear Magnetic Resonance
o-tol = 2-methylphenyl
PEG = poly(ethylene glycol)
Ph = phenyl
REM = Regenerated Michael (linker)
tBu = *tert*-butyl
THF = tetrahydrofuran
TPFPP = 5,10,15,20 –tetra(pentafluorophenyl)porphyrin
TPP = 5,10,15,20 - tetraphenylporphyrin
Ts = tosyl
UV = ultraviolet

1 Introduction

1.1 Pharmaceutical development – the need for speed

1.1.1 Overview of the drug development process

The development of a marketable new drug is a long and complicated process. From the time the idea is first realised until the final product is ready for approval by the authorities the average time span is 10-12 years and the costs exceed US\$ 800 million. (Figure 1).^{1,2}

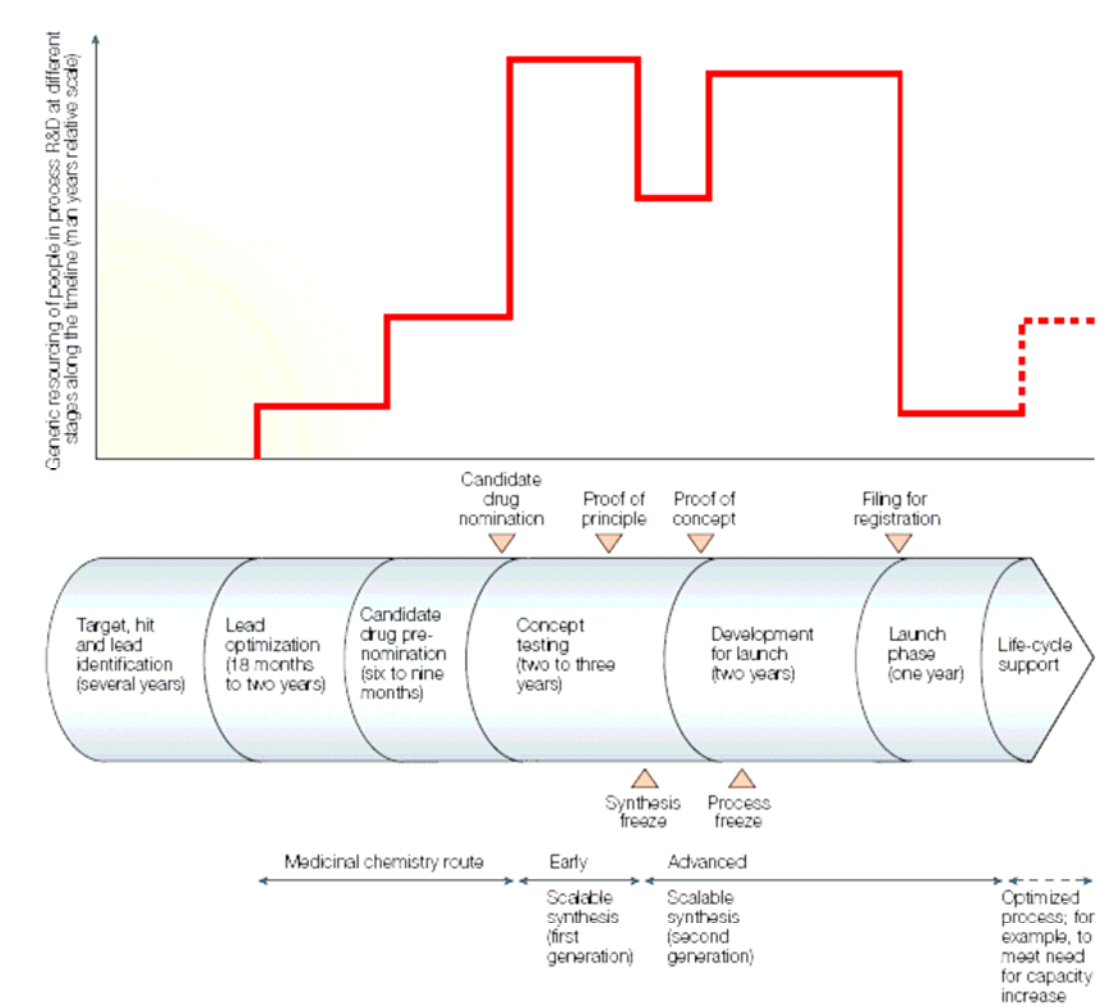


Figure 1: A schematic overview of the Drug Development process, with a scheme of the intensity of Process Chemistry work at different stages.¹ Note that the workload is highest in the initial stages of development.

The vast majority of the drug candidates nominated for further development are eventually discontinued on the grounds of not being active enough or having undesirable side effects. As an estimate based on the Research & Development process at H. Lundbeck A/S, only 3-4 % of the initial compounds to enter the development phase will ever develop to a marketable drug (Figure 2).³⁻⁵

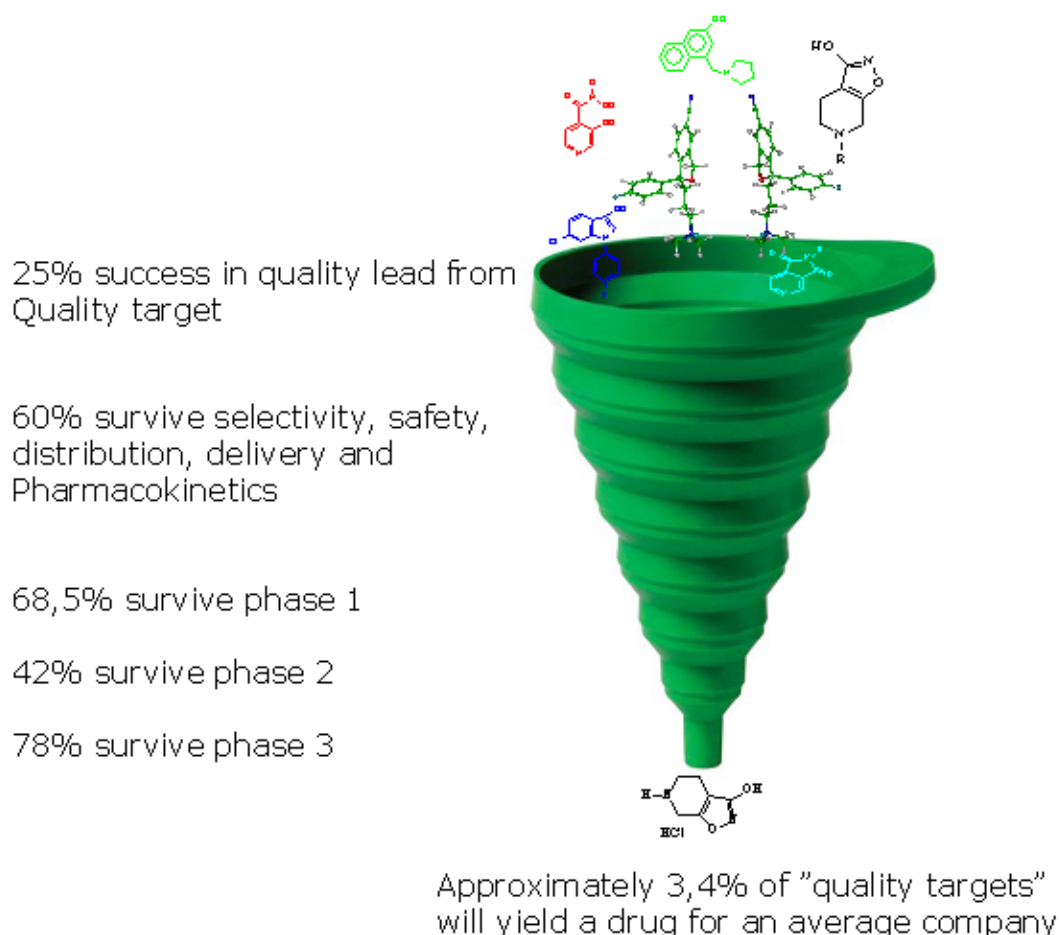


Figure 2: The drug development “funnel”. Only about 3-4 % of the compounds selected for development make it to marketing.³

The pharmaceutical industry today is facing pressure from many sides. The increased competition means that new drugs have less time to prove their worth before new and better alternatives are marketed. Increased concerns over drug safety, and rising costs of medical care have led to higher demands for documentation by the authorities, mainly in the form of expensive clinical trials, and demands for lower prices. Furthermore generic competition is becoming more and more aggressive.^{6,7}

In the highly competitive climate of the pharmaceutical market, it is more important than ever that a pharmaceutical corporation is able to identify and develop new compounds into marketable drugs fast – and to identify and discontinue unmarketable drugs and compounds as soon as possible.

1.1.2 The role of the Process Research department

The department of Process Research occupies a central role in the drug development process. When a new potential drug compound is transferred to the Process Research department it is said to move from the discovery phase to the development phase. This is very fitting as the resources and expenses associated with the project rise dramatically after this point.¹

When a compound is selected for development the mission of Process Chemistry is twofold:

1. To produce 200-300 g of the compound as soon as possible for the big four weeks toxicology test.
2. To develop a route suitable for kg scale production according to the rules for Good Manufacturing Practice (GMP) and by that route make 20 kg of compound for the first doses in humans.

The primary objective during the preceding Discovery phase, by contrast, is to produce a large range of compounds of interest in relatively small amounts within a short period of time. As a result, it is unsurprising that the synthetic methods used to produce the compounds at this stage are unsuited for larger scale production. Typical problems include low yielding or highly exothermic reactions, the use of toxic, sensitive or expensive reagents, and a significant focus on chromatography for all solution-phase purification steps. Therefore, in the development phase a prime focus is on developing new routes or methods that can be used for multi-gram and kg-scale synthesis of the compound. This consists in part of finding cheaper and less toxic starting materials and reagents, and purification methods more amenable to scale up (such as crystallisation). This can be a difficult process, and therefore has the risk of becoming a bottleneck in the overall development process.

As in every step of pharmaceutical discovery and development some compounds will always fail the initial four-week toxicology test and be discontinued. An established flexible technique for fast initial scale-up to about 200 g would therefore be desirable, as it would potentially lower the process research work cost involved in developing a whole new kg-scale synthesis route for a drug, which does not make it to clinical testing.

One common technique, which was invented with the specific purpose of lowering the time for synthesis work, is the solid-phase chemical synthesis technique.

1.2 Solid phase Chemistry

1.2.1 The concept of solid phase chemistry

“Such a system offers four main advantages: it simplifies and accelerates the multistep synthesis because it is possible to carry out all the reactions in a single reaction vessel, and thereby avoid the manipulations and attendant losses involved in the repeated transfer of materials; it avoids the large losses that normally are encountered during the isolation and purification of intermediates; it can result in high yields of final products through the use of excess reactants to force the reaction to completion; and it increases salvation and decreases aggregation of the intermediate products.”⁸

When Prof. Merrifield described this, for a synthetic chemist, almost utopian system in his Nobel lecture, it had already been known and used for more than 20 years, and had become a routine technique in the synthesis of peptides and other biopolymers.^{9, 10} The idea was as simple as it was ingenious. Peptide synthesis had been in rapid development since 1953, where du Vigneaud had accomplished the first peptide synthesis,¹¹ but the development was hampered by the time-consuming procedures and the low solubility of heavily-protected intermediate peptides. By linking the peptide covalently to a solid support of polystyrene cross-linked with divinyl benzene (later known as Merrifield resin), the intermediate tedious and difficult purification steps were replaced by simple filtration (Figure 3). In this manner, Merrifield and his co-workers were able to synthesize large peptides such as bovine insulin in a matter of days.¹² The method could even be automated, leaving the chemists even more time to think great thoughts.^{13, 14}

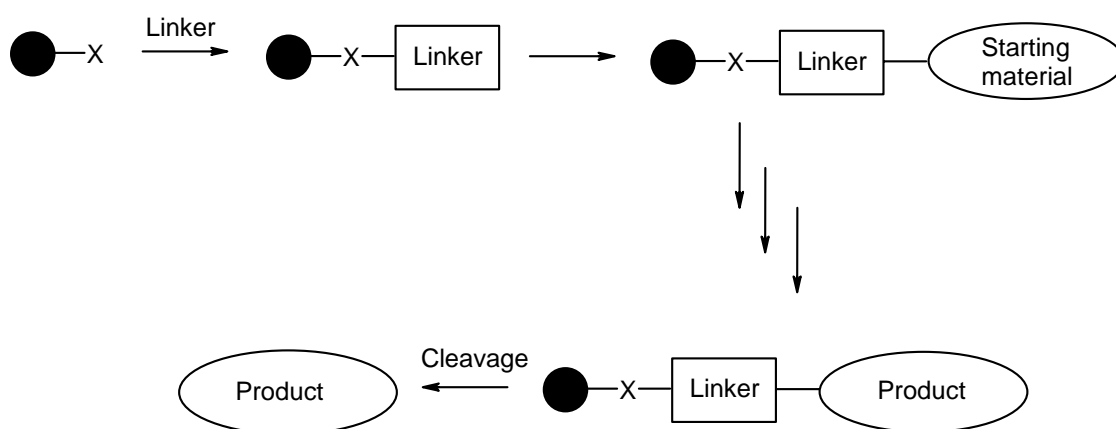


Figure 3: Traditional solid-phase synthesis. The starting material is immobilized on the reactive polymer (usually through some kind of added functionality, a linker) and the reaction steps are performed with filtration and wash between each step. The product is then cleaved from the resin, similar to deprotection in solution- phase reactions.

In spite of these obvious advantages, solid-phase chemistry was for a long time almost exclusively used for the synthesis of biopolymers such as peptides and oligonucleotides,¹⁵ although a few examples of small-molecule synthesis were attempted.¹⁶

The reason for this reluctance to apply the method more broadly might be rooted in the limited number of analysis methods available to follow the reactions in solid-phase chemistry. The usual chromatographic techniques for reaction monitoring are unavailable, and extra cleavage steps must be added, if a traditional analysis of intermediates is desired. Indeed one of the referees on Merrifield's original paper expressed the opinion that solid-phase synthesis "should be shunned, as it violated the basic principles of synthetic organic chemistry, i.e. isolation and characterization of intermediates."¹⁰

This changed during the nineties when the development of new screening methods made it possible to screen millions of compounds for biological activity every year. The need for a technique, able to meet the demand for a large number of potential drugs outweighed the disadvantages and solid-phase combinatorial chemistry soon became an important tool in the pharmaceutical industry.^{17, 18}

1.2.2 Combinatorial chemistry and high throughput screening

Combinatorial chemistry is, simply put, the change from linear synthesis to branched synthesis. Instead of a synthesis where A is reacted with B to give C, A is reacted with a multitude of different compounds, thereby increasing the output exponentially with each step (Figure 4). Such a large number of reactions need to be performed with some degree of automation in order to be efficient, and here the easily-automated solid-phase technique held great potential.^{17, 19}

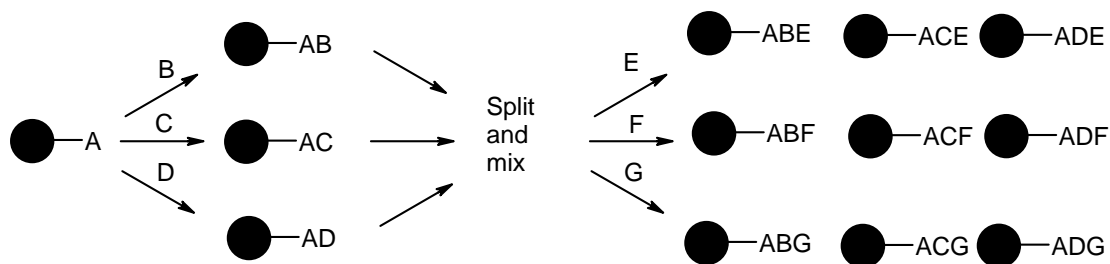


Figure 4: Combinatorial chemistry through the popular "split-and-mix" strategy, where a solid-phase bound starting material (A) is reacted with three different compounds (B, C and D). The resins are then pooled and split up again for reaction with three new compounds (E, F, and G) resulting in the generation of nine new, structurally related compounds simultaneously.

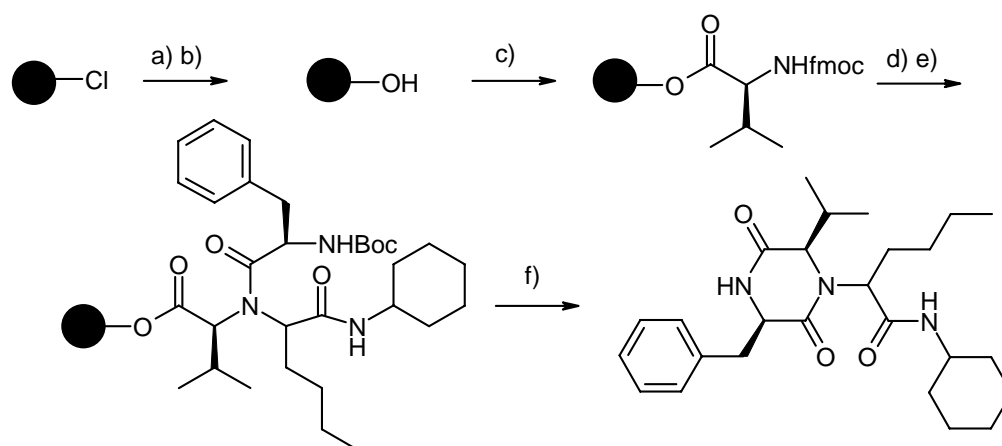
Not surprisingly the idea of combinatorial chemistry first emerged in peptide chemistry, where a number of different building blocks with comparable chemistry, the amino acids, were readily available. Peptides and other biooligomers are, however, not usually the best drug candidates, due to their low bioavailability and stability.¹⁷ The first solid-phase combinatorial synthesis of a small biologically-active molecule was published in 1992 by Bunin and Ellman²⁰, leading to a very rapid

development in the field of solid-phase synthesis of small molecules (MW < 600).^{15, 17, 21, 22}

1.2.3 Multigram- and kg-scale solid-phase synthesis

Multigram- and kg-scale synthesis of biopolymers on solid-phase has been a well-established technique for many years.^{23, 24} Today large-scale syntheses of biopolymers such as peptides²⁵ and oligonucleotides²⁶⁻²⁸ on solid phase are carried out routinely. Recently the first example of a multi-ton, partially solid-phase synthesis of a peptide-based drug (the Roche anti-HIV drug Fuzeon) was published.^{29, 30}

Larger-scale synthesis of small drug molecules on solid phase, however, remains a relatively unexplored field. Dr. Stephen Raillard of Affymax published his pioneering work on the scale-up of small molecule synthesis in 1999,³¹ the idea being to save time in development, by capitalizing on the experiences gained in the combinatorial (solid-phase) discovery phase. Using high loading Merrifield resin (4.4 mmol/g), he and his co-workers produced three reasonably-complicated nitrogen heterocycles in high yield and purity over the course of a week – including the time used for linking the starting material to the resin (Scheme 1).

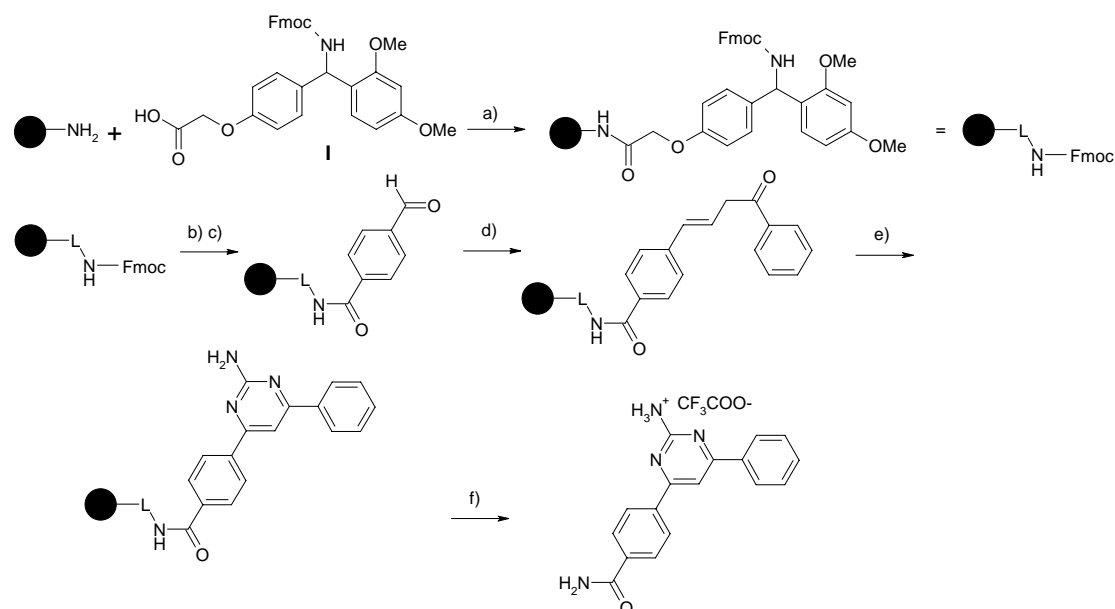


Scheme 1: Solid-phase synthesis of a diketopiperazine on multigram-scale by Ugi – reaction after Raillard *et al.*³¹ a) Merrifield resin (3.9 mmol/g), CH₃OOK (1.5 equiv), 2-methoxyethanol, reflux, 16 h. b) NaOH (2 equiv), dioxane/water (1:1), reflux, 16 h. c) Fmoc-valine (3 equiv), pyridine (3 equiv), 2,6-dichlorobenzoyl chloride (3 equiv), NMP, r.t., 24 h. d) 20% piperidine/NMP, r.t., 30 min. e) n-pentylaldehyde (3 equiv), Boc-phenylalanine (3 equiv), cyclohexyl isocyanide (3 equiv), DCM, r.t., 15 h, f) (1) trifluoroacetic acid/DCM (1:1); r.t., 1h; (2) Acetic acid (1%), MeCN, r.t, 2 x 3 h; (3) 4% triethylamine/MeCN. Yield (from hydroxyl resin) 79 %

Raillard *et al.* made a number of important observations in this study:

1. The established literature procedures could be used on larger scale with only minor modifications
2. The simplified washing procedures greatly reduced the total synthesis time.
3. Multistep reactions could be completed within a few days, yielding product with a purity > 90 %
4. High concentrations of compound could be employed, meaning that low excesses of reagent (1.5-2 equiv) could be used without compromising yield and purity of the final product.

A later synthesis by Meisenbach *et al* of Novartis³² took a route originally developed for a combinatorial library synthesis, and scaled it to > 70 g scale (55 %) on modified Merrifield resin with few complications (Scheme 2).



Scheme 2: Meisenbach *et al*'s 70 g-scale solid-phase synthesis of a pyrimidine:³² a) Aminopolystyrene (4.48 mmol/g), Linker **I** (1.5 equiv), DIC (1.8 equiv), DMF, r.t., 16 h; b) 20% diethylamine in DMF, r.t., 2 x 15 min.; c) 4-Carboxybenzaldehyde (1.3 equiv), HOBt (1.3 equiv), DIC (1.5 equiv), DMF, r.t., 16 h; d) Acetophenone (1.5 equiv), LiOH (0.5 equiv), THF/methanol (4:1), 23°C, 1.5 h.; e) Guanidine, hydrochloride (6 equiv), NaOEt (6 equiv), DMA, 100°C, aerobic atmosphere, 16 h; f) 20% trifluoroacetic acid in DCM and recrystallization from ethanol/water (9:1). Yield 55% overall

A solution-phase route that was developed for comparison purposes gave lower yields (21-34%) on a similar scale. The principal problem observed in solution was the low solubility of the hydroxyketone intermediate, a phenomenon not encountered in the solid-phase route.

As these two examples have shown, performing multi-gram scale chemistry on solid-phase holds many potential advantages as a rapid method for the generation of multiple grams of a small molecule.

However, the disadvantages of solid-phase chemistry are still present. It is not possible to isolate and characterize the intermediates, and the progress of the reactions cannot be monitored by the traditional chromatographic methods.

For scale-up using solid phases, other problems arise: large-scale solid-phase synthesis is usually performed in specialized equipment, such as reactors with fritted bottoms (the method used in the above mentioned examples) or as on-line automated synthesis, neither of which are common items in a scale-up or development laboratory. In addition, although the cost of standard Merrifield resin has dropped in recent years it would still be a significant extra expense.

In order for a solid-phase route to be feasible as a routine technique on a larger scale, these problems will have to be adequately addressed.

1.3 Resins in solid-phase chemistry

1.3.1 The properties of the solid phase.

The properties of the solid-phase used to support a chemical reaction are of great importance. The solid-phase can be considered an extra phase in which the reaction takes place, as most of the active sites of a resin are typically inside the bead. New parameters such as the ability of a reagent to diffuse into the bead, and reactions with the polymer framework must therefore be taken into consideration.³³

The typical resins used in solid-phase synthesis today are based on the cross-linked polystyrene resin originally developed by Merrifield.¹⁹ Resin beads of a suitable size for reaction purposes were originally obtained by grinding down the polymerized product, but more uniform spherical beads are obtained nowadays by suspension polymerization, where the beads polymerise as a suspension in an inert media. With a careful choice of reaction conditions a high degree of control over the bead size can be obtained.^{15, 34} Typical bead size (dry beads) is in the range 0.04 – 0.15 mm, however for some purposes, a larger bead size, so called macrobeads, is feasible.^{35, 36}

1.3.2 Swelling

One of the most important parameters of a resin is the ability of the beads to expand in the solvent used for the reaction, thereby allowing efficient diffusion of reagents to the reactive sites. This property is referred to as swelling, as the bead size increases dramatically in such a favourable solvent.^{19, 33} As previously mentioned most of the active sites in a resin bead are placed inside the resin, meaning that the ability of reagents to enter the resin is crucial. If the polymer is sufficiently swollen, reaction rates with reasonably non-polar reagents are usually not diffusion controlled and are therefore independent of bead size.^{37, 38} The swelling of resins can be conveniently measured by suspending the resin in the solvent in a fritted syringe for a while, then suck it dry and measure the volume of the resin (The syringe method).^{39, 40}

Standard Merrifield resin is hydrophobic, and does not swell appreciably in a number of common solvents, including water and ethanol.¹⁹ A lower degree of cross-linking will increase the swelling, but this tends to decrease the mechanical stability of the beads.³³ Although the use of standard Merrifield resin on a larger scale is feasible in spite of this drawback, it would be a huge advantage from a process chemistry point of view if non-toxic solvents such as water and ethanol could be used.

1.3.3 Hydrophilic polymers

Soluble-supported synthesis, where the reagent is bound to linear (not cross-linked) poly(ethylene glycol) (PEG) or another soluble polymer^{19, 41} is one way of circumventing the swelling problem. The large polymer chain (>2000 g/mol) keeps the compound in solution until the synthesis is finished. The polymer is then precipitated by adding a solvent in which it is insoluble (e.g. heptane), after which it is possible to wash away impurities as with conventional solid-phase synthesis.

In 1991 Dr. Ernst Bayer reported that he had linked PEG chains to Merrifield resin, thereby creating a solid phase compatible with the same broad spectrum of solvents as PEG itself.⁴² Various PEG-grafted polystyrene resins, such as Tentagel™^{43, 44} and Argogel™,⁴⁵ are still frequently-used in solid-phase chemistry, due to their good swelling properties and convenience of use (Figure 5).

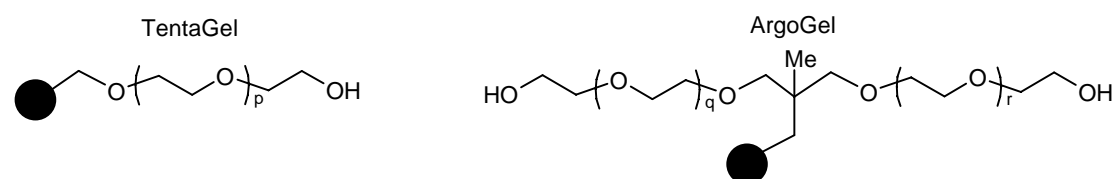
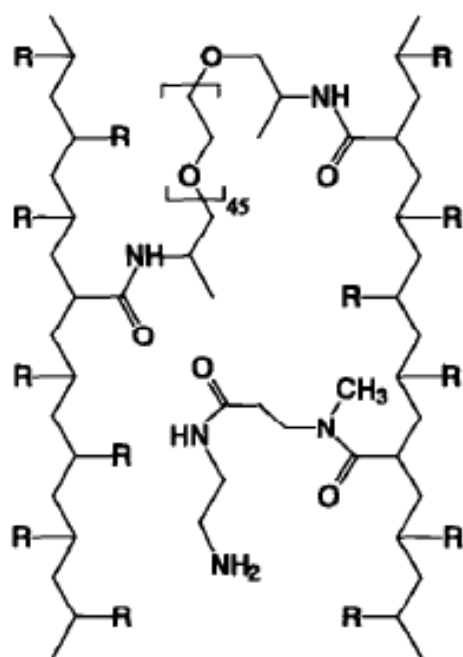


Figure 5: Tentagel™ and Argogel™.⁴²⁻⁴⁵ Polystyrene resins grafted with PEG for better swelling properties. Argogel™ does not contain a benzylic ether group, and is therefore more chemically stable.

Polystyrene-PEG grafted resins, however, hold a number of drawbacks, the main ones being low chemical and mechanical stability, low loading and high cost, which generally precludes their use in the scaling up of small molecule solid-phase synthesis.¹⁹

Various derivatives of polyacrylamide have been used frequently as solid supports and are a cost efficient alternative to Polystyrene-PEG,^{19 46 47} but they too suffer from low mechanical stability, which make them unsuitable for some applications, such as continuous flow synthesis⁴⁸ and on-resin scale up.

In the late nineties Meldal *et al.* developed a highly-stable hydrophilic resin based on Polyacrylamide cross-linked with PEG-based macromonomers (PEGA) (Figure 6). This new resin type was compatible with both polar and non-polar solvents, highly mechanically stable and comparatively cheap to produce.^{39, 49-51} It was later marketed by VersaMatrix A/S under the tradename Versabeads A™.



4 $R = -CON(CH_3)_2$

Figure 6: Structure of the PEGA resin (Versabeads A)⁵¹

1.3.4 The SPOCC resin

The capacity of PEGA was still low, with an average loading of 0.2-0.4 mmol available amino groups per gram, and the presence of amide groups in the framework means that the resin was not compatible with all chemical conditions (e.g. hydrolytic).

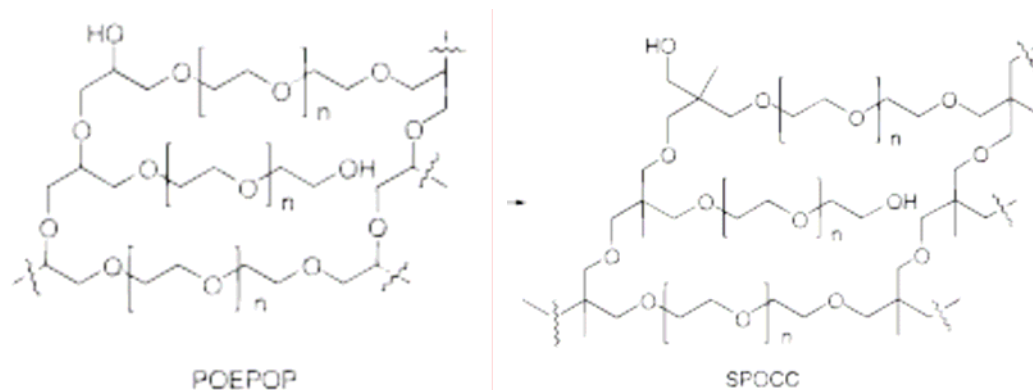


Figure 7: Structure of epoxide based resin POEPOP and oxethane based resin SPOCC.⁵⁴

To circumvent this problem Meldal *et. al.* developed a new kind of polymer beads based solely on cross-linked PEG, through the ring opening polymerization⁵² of epoxide- and oxethane-capped PEG-based macromonomers. Of these two polymers, POEPOP⁵³ and SPOCC⁵⁴, SPOCC is the most stable, as it contains only alkane bonds and primary ether bonds (Figure 7).

In later studies, where the properties of SPOCC and POEPOP were compared to traditional Polystyrene-PEG resins, the physical properties of the non- polystyrene containing resins were fully comparable to the much more expensive commercial brands (Table 1, Table 2). The diffusion rate of a test reagent was found to be somewhat slower in the non-polystyrene resins, but still in the same order of magnitude.⁵⁴⁻⁵⁶

| | Amino- methylated polystyrene | TentaGel | ArgoGel | POEPOP 400 | SPOCC 400 | SPOCC 1500 |
|--------------------------------|-------------------------------------|----------|---------|---------------|--------------|---------------|
| Bead size (µm) | 75-150 | 130 | 120-230 | 300-500 | 300-500 | 300-500 |
| Swelling in water (mL/g) | - | 3.8 | 2.8 | 2.5 | 3.5 | 6.0 |
| Swelling in THF (mL/g) | 7.2 | 2.8 | 5.0 | 2.5 | 2.5 | 4.5 |
| Swelling in MeCN (mL/g) | 6.7 | 1.8 | 4.4 | 2.5 | 2.5 | 4.5 |

Table 1: Comparison of swelling properties of various commercially available resins with POEPOP 400 and SPOCC 400 and 1500 (values approximated from figure).⁵⁵

| | Bead size (μm) | Loading (mmol/g) | Amount (g) | Price (€) | Price/equiv (€/mmol) |
|------------------------------------------|--------------------------------|---------------------|---------------|-------------------|-------------------------|
| Rapp hydroxymethylated polystyrene | 200-400 ^a | 1.5 | 100 | 360 | 0.240 |
| TentaGel | 130 | 0.3 | 100 | 1010 | 33.667 |
| ArgoGel | 120 | 0.5 | 100 | 1203 ^b | 24.06 ^b |
| Versabeads O | 100 -400 | 2.0 | 100 | 739 | 0.370 |

Table 2: Price comparison for a number of standard resins. It should be noted that the commercially available TentaGel and ArgoGel bead sizes are usually much narrower distributed than Merrifield and Versabeads, a factor which contributes to the high price.^a mesh size. ^b Price converted from US\$ (1US\$ = 0.83 €)

For this study, three different SPOCC polymers were synthesized: SPOCC-400, SPOCC-900 and SPOCC-1500. The numbers refer to the molar weight of the PEG chain on the macromonomer. The polymers with longer chains showed better diffusion properties than those with shorter chains. The longer-chained monomers showed a tendency to form emulsions and aggregate during polymerization, which was later corrected by developing a new polymeric pentamethyldisiloxane surfactant, Polysurf.⁵⁷ (figure 10)

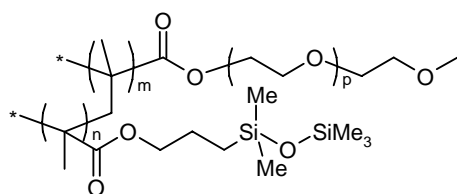


Figure 10: Polysurf general structure.⁵⁷

VersaMatrix A/S later marketed the SPOCC resins under the tradename Versabeads OTM, with PEG chain lengths of 400 and 2000, with hydroxyl loadings in the area from 0.5 to 2.5 mmol/g.⁵⁸⁻⁶⁰ With their high mechanical stability, their high loading, their tolerance towards most reaction conditions and their reasonable price, the Versabeads can potentially be used in scaling up on solid phase, as described by Raillard and Meisenbach.^{31,32}

1.4 Functionalization – Linkers for large-scale solid-phase synthesis.

A crucial point in any solid phase synthesis is the linker, the functionality that binds the molecule being synthesized to the resin. The linker can in many ways be compared to a protecting group in that its prime qualities are that it is stable under the reaction conditions employed in the synthesis and can be cleaved under conditions that do not adversely affect the product. As with protection groups, a number of different linkers have been developed over the years, for all kinds of functionalities and purposes.^{19, 61}

A linker for use in the solid-phase synthesis of small molecules on a larger scale must have some additional qualities. For economic reasons it must be cheap and easy to make and preferably reusable. It cannot be too large, as it would then decrease the loading of the resin and thereby reduce its cost-effectiveness. It should still be stable to the reaction conditions, but the cleavage conditions must be amenable for large-scale synthesis using standard, general-purpose reactors. Examples of linkers that would be unsuitable for this purpose include many of the old linkers for peptide synthesis which were cleaved by hydrogen fluoride (a chemical generally to be avoided on larger scale) and photocleavable linkers, where the cleavage reaction is very difficult to scale.¹⁹

1.4.1 Carbamate and Wang-carbamate linker

The carbamate linker, generated from a resin-bound nucleophilic group and either phosgene or a phosgene equivalent, is a very popular linker for amines (Figure 11). As carbamates are also frequently used as protection groups in solution-phase chemistry, much literature exists on the formation and cleavage of various carbamates. It is not reusable, but as it is very small and comparatively cheap to make this is not really a problem.

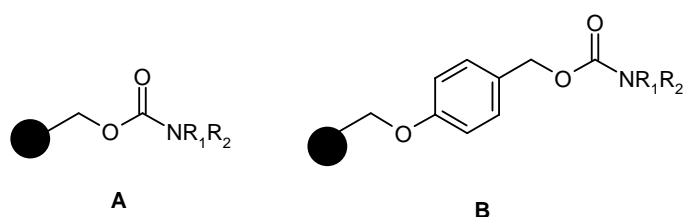
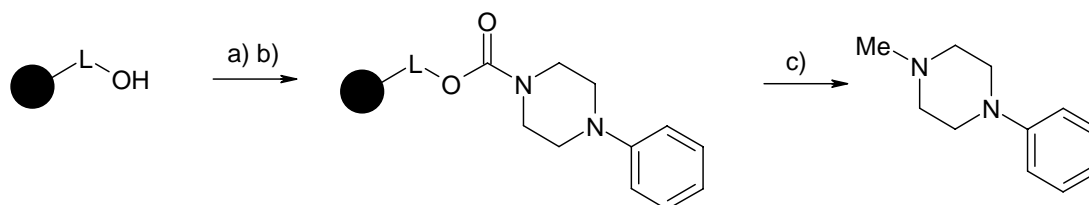


Figure 11: (A) Carbamate linker and (B) Carbamate linker combined with Wang linker

The vast majority of the literature on solid-phase synthesis concerning the carbamate linker uses it in conjunction with the Wang linker, which gives an acid-labile combination, similar in reactivity to the *p*-methoxybenzyl carbamate group in solution chemistry.⁶² Standard Wang-linker carbamate cleavage conditions are 50% trifluoroacetic acid in dichloromethane.¹⁹

As the Wang linker is one of the most popular linkers in use today¹⁹ its chemistry is well known, and many literary procedures exist for attachment of Wang- and Wang-type linkers to PEG and PEG-based supports, both through nucleophilic addition or Mitsunobu reaction.^{45, 63-67}

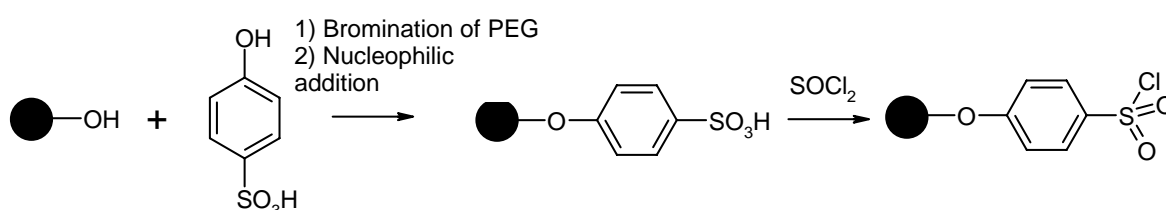
An additional advantage of the carbamate linker is the possibility for cleavage under reductive conditions, thereby utilising the carbonyl carbon to create a tertiary (or secondary) methyl amine (Scheme 3).⁶⁸



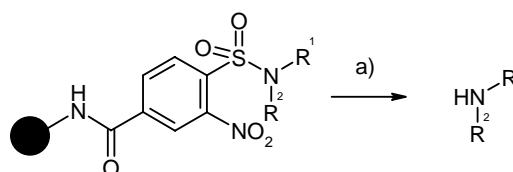
Scheme 3: Ho and Kukla's synthesis of 1-methyl-4-phenylpiperazine on Wang/Merrifield resin⁶⁸ a) N-methylmorpholine (3 equiv), 4-nitrophenyl chloroformate (3 equiv), r.t., overnight. b) 1-phenylpiperazine (5 equiv), diisopropylethylamine (5 equiv), DMF, r.t., overnight. c) Lithium aluminium hydride (10 equiv) in THF, 60°C, 14 h. Yield 84% (GC purity >95%)

1.4.2 Sulphonic acid linker

Derivatives of phenyl sulphonic acid are well-known protection groups for amides.⁶² As the cleavage reaction is a simple hydrolysis the potential for reusability is clear. Resin-bound sulphonic acids are mainly used as scavengers for the removal of excesses of nucleophilic reagents, but a few examples of sulphonic acids as linkers for the solid-phase synthesis are known in literature (Scheme 4, Scheme 5).⁶⁹⁻⁷⁵



Scheme 4: A possible route to a sulphonyl chloride linker on SPOCC, originally performed on PEG soluble support.⁷⁵



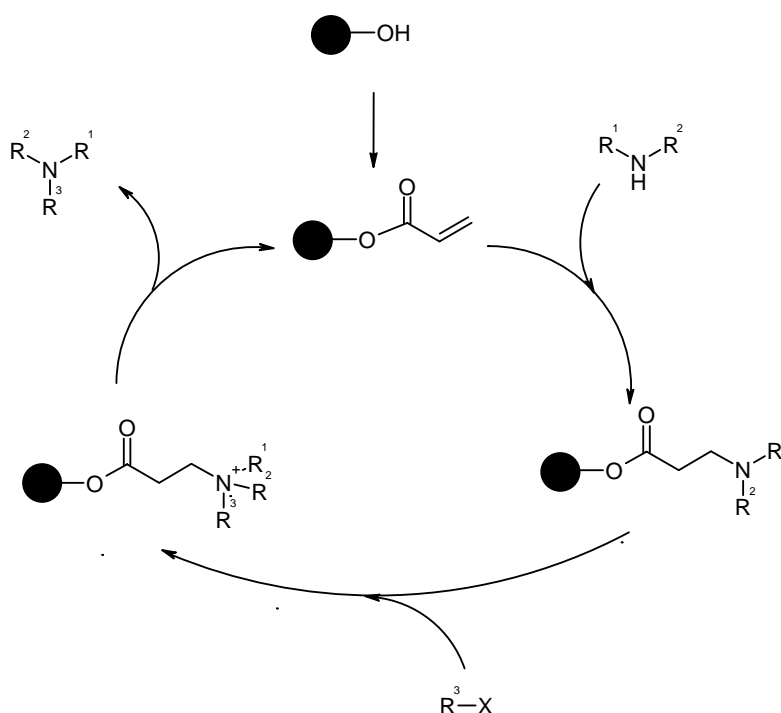
Scheme 5: A sulphonyl amine linker in the synthesis of amines.⁶⁹ a) thiophenol, K₂CO₃, MeCN.

1.4.3 boc- equivalents on resin

The boc group is a very versatile protection group in organic chemistry. Examples of a solid phase analogue to the boc-protection group exist,^{76, 77} but as boc in solution is known to eliminate isobutene upon cleavage the easy reusability of this linker is a bit questionable.

1.4.4 The REM linker

The REM linker (REgenerable Michael linker) is based on the Michael-addition to α,β conjugated double bonds, and it is one of the few linkers available that produces tertiary amines upon cleavage. After the molecule is constructed on the resin, the nucleophilic atom used as an attachment point is made susceptible to elimination (typically Hoffmann elimination for amines, typically by quaternization), and cleaved under basic conditions (Scheme 6).



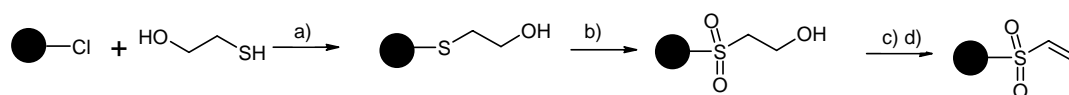
Scheme 6: Synthesis of tertiary amines, here shown with an acrylic acid based REM linker on Merrifield resin after Morphy *et al.* Modifications on the resin bound amine before quaternization are not shown.⁷⁹

The original REM linker was based on acrylic acid, and has been used for the synthesis of number of compounds. The group at Organon, which originally developed the linker, has done extensive research on its properties, and synthesised several tertiary amines through electrophilic addition, transesterification and Stille

chemistry.⁷⁸⁻⁸² Of especial interest in the context of Versabeads is their discovery that water is a good medium for the quaternization reaction.⁸¹

Other groups have worked with REM linkers, mainly in the synthesis of tertiary amines⁸³⁻⁸⁷. A number of other kinds of compounds have been synthesised on an acrylic acid-based REM linker, including γ -lactams through intramolecular Mitsunobu,⁸⁸ purines⁸⁹ and macrocycles.^{90, 91} Experiments with resin reuse have shown good stability over 5 cycles.⁸⁷

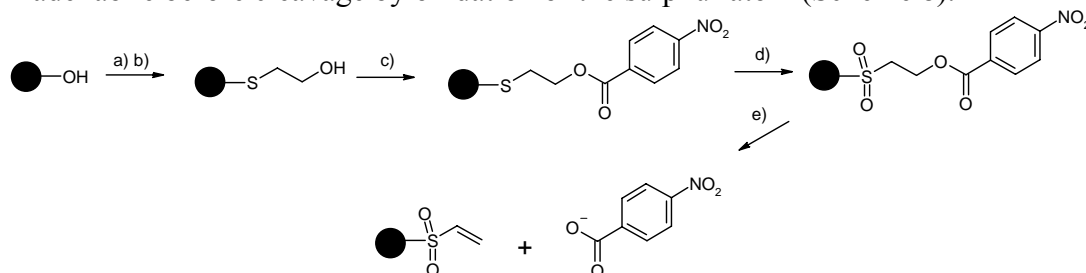
Other Michael acceptor-based linkers have been developed with good results.^{92, 93} The most popular alternatives to acrylates are based on vinyl sulphones, which are inherently more stable to most reaction conditions than esters. Gani *et al.* made a sulphone based REM linker by oxidation of a resin-bound thioalcohol, followed by elimination (Scheme 7).^{94, 95}



Scheme 7: The synthesis of vinyl sulfone linker.⁹⁴ a) mercaptoethanol, Cs_2CO_3 , DMF, r.t., 3 days. b) 3-chloroperbenzoic acid, DCM, r.t., 12 h. c) Mesityl chloride, pyridine, DCM, r.t. 2 h. d) base.

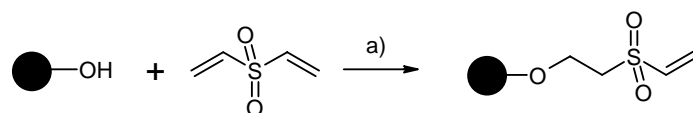
This linker has later been used in Pictet-Spengler synthesis on solid support.^{96, 97}

An equivalent to this linker has been made on SPOCC resin through a similar procedure. Here the objective was to make a safety-catch linker, where the linker is made labile before cleavage by oxidation of the sulphur atom (Scheme 8).⁹⁸



Scheme 8: Synthesis of a vinyl sulfone linker on SPOCC as residue from a safety-catch linker.⁹⁸ a) mesityl chloride, pyridine, DCM. b) 2-thioethanol, Cs_2CO_3 , DMF. c) 4-nitrobenzoic acid, pyridine, DCM. d) 3-chloroperbenzoic acid, DCM. e) DBU, DCM.

Another approach to the sulphone-based REM linker was that of Hainonen *et al.*, who attached divinyl sulphone to hydroxyl-functionalized resin (Scheme 9).^{99, 100} The addition of divinyl sulphone to PEG is a known reaction, as it has been investigated as a way to link PEG to proteins as a means of increasing the stability of the latter.^{101, 102}



Scheme 9: Synthesis of a REM-type linker from hydroxymethyl polystyrene and vinyl sulphone.⁹⁹ a) Divinyl sulphone (excess), DBU (excess), r.t. overnight. Yield 40-50%

The REM-type linkers are specifically designed for reuse, and hold great potential for the purpose of large-scale solid-phase synthesis of amines. One limiting factor is, however, that the choice of quarternization agent seems to be restricted to the more reactive alkyl halides. An example of cleavage through an Oxidation-Cope rearrangement (to give hydroxylamines) is known,⁹² but otherwise good yields have mainly been obtained only with methyl-, allyl-, benzyl- and other activated halides.

1.4.5 Triazene-based linkers

Bräse *et al.* have developed two reusable triazene-based linkers, Triazene 1 for the synthesis of arenes¹⁰³ and Triazene T2 for the synthesis of amines.¹⁰⁴

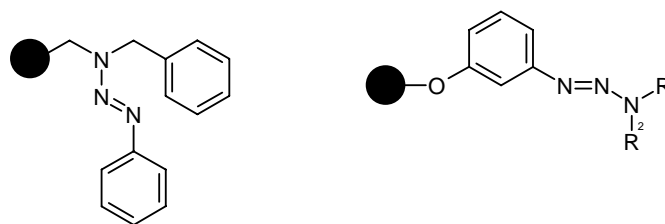


Figure 12: Triazene-based linker T1 (for aromatic compounds) and T2 for amines, amides and ureas on Merrifield resin.^{103, 104}

Triazene T2 is comparatively simple to make, is reusable and its use in synthesis is well known.¹⁰⁵⁻¹⁰⁸ In 2004 a convenient large-scale synthesis of this type of linker was published.¹⁰⁹

1.5 Analytical methods in solid-phase chemistry

1.5.1 Analysis methods in general

A major difficulty in solid-phase synthesis is the monitoring of the reactions and the characterization of the resin-bound intermediates and products, as the usual chromatography-based analysis methods are not available. Although a number of analysis methods have been developed successfully for the analysis of resin-bound compounds,^{19, 110-114} all monitoring and analysis of a solid phase reaction can only be indirect, as no compounds are isolated between steps.

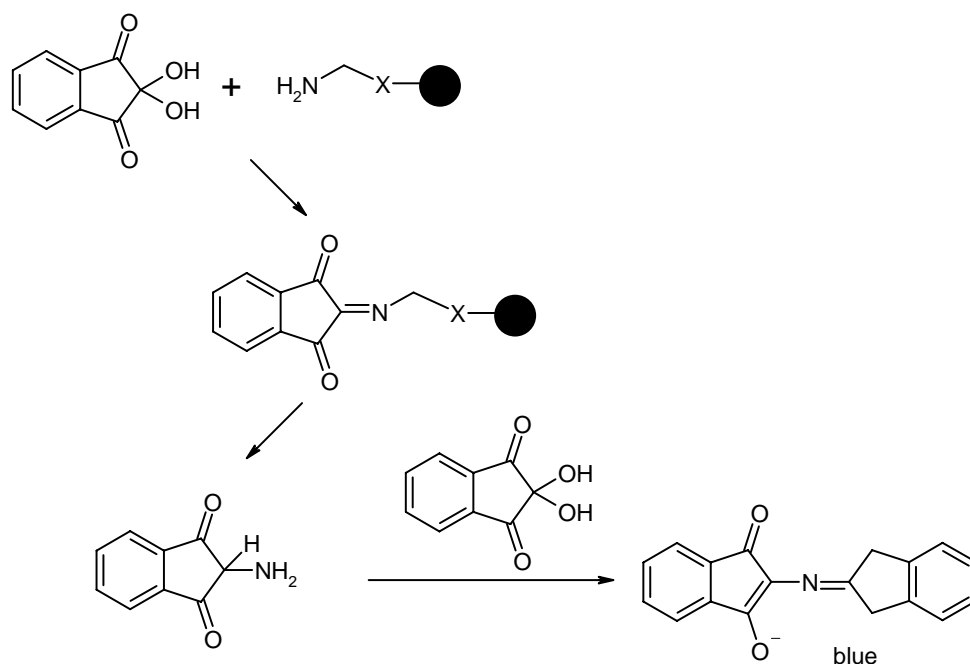
For this project it was important to have a suite of reliable, multi-functional analysis methods, which could be easily performed without the use of special equipment not present in a typical scale-up and development lab.

1.5.2 Cleave and analyze

Treating a small sample of resin with a cleaving agent is an obvious way of getting information about the intermediates, and has been practiced with success in the synthesis of heterocycles on solid phase.^{115, 116} Methods that require very small cleavage samples have been developed.¹¹⁷ These methods are, however, time consuming and laborious, and require an additional step in the process, which might tamper with intermediates not stable to cleavage conditions. They are therefore best suited for monitoring of well-defined solid-phase reactions, such as peptide synthesis.

1.5.3 Staining reagents

Adding a reagent which changes colour upon reaction with certain functional groups is a very common qualitative (and in some cases quantitative) method of reaction monitoring, as it is fast, easy to carry out and does not require special equipment. The Kaiser-ninhydrin test for free amino groups has been a standard monitoring method in solid-phase peptide synthesis for many years (Scheme 10).^{118, 119}



Scheme 10: Mechanism of the Kaiser-ninhydrin test.¹¹⁹

The Kaiser test is only sensitive to primary amines. Secondary amines and primary aromatic amines can be detected with other reagents, e.g. the chloranil and isatin tests.¹²⁰⁻¹²² Chloranil has also been used for diffusion studies, by studying amino functionalized beads acylated at various reaction times, then stained with chloranil under microscope.⁵⁶

Other reagents have been developed for hydroxyl-,^{123, 124} thio-,¹²⁵ carbonyl-,¹²⁶ and carboxyl-¹²⁷ groups, as well as for activated halogens¹²⁸ The topic has been covered in several reviews.^{19, 110, 129, 130}

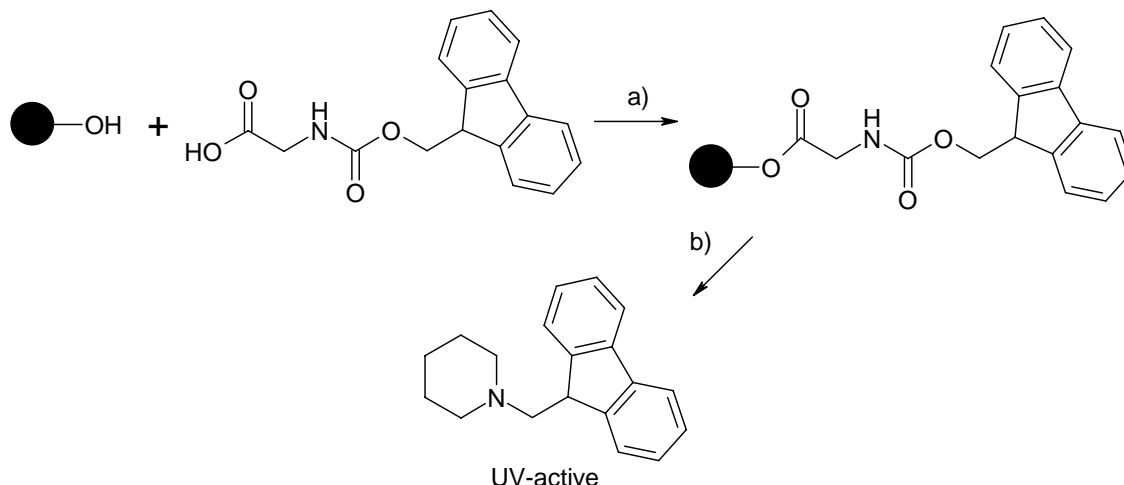
On a larger scale, where it is generally not favourable to drive reactions to completion with large excesses of starting material, the staining reagents might be too sensitive, as most of them are designed to detect very small amounts of functional groups (For instance the Kaiser test can detect below 1 μmol of amino groups¹¹⁹) An attempt was made to confirm the formation of the carbamate linker through addition of ethylene diamine with a subsequent Kaiser test, but this proved unsuccessful as even unreacted Versabeads O gave positive test for amino groups. Later analysis by VersaMatrix A/S revealed that some amino group contamination was present on resin, possibly from the acetonitrile used as solvent in the polymerization step. This problem has later been corrected, and peptide synthesis on Versabeads has been successfully monitored with the Kaiser test.⁵⁸ The initial negative result discouraged the use of staining reagents for further reaction monitoring in the course of the project.

1.5.4 Addition and cleavage of UV-active compounds

The addition and subsequent cleavage of a compound with known spectrophotometric properties is a well-established method for monitoring in solid-phase synthesis.^{110, 129}

The common peptide protection group 9-Fluorenylmethoxycarbonyl (Fmoc)¹³¹ is commonly used for this purpose, as it forms a range of easily detected species upon cleavage. A real-time monitoring method based on Fmoc cleavage has been developed for peptide synthesis.¹³² The Kaiser test has been used for this purpose as well,¹¹⁹ although more reliable reagents have since been developed.^{110, 133}

The loading of the Versabeads was determined by the well-known Fmoc-glycine method, where Fmoc protected glycine is attached to resin, followed by cleavage and analysis of the adduct in solution (Scheme 11).^{134, 135}



Scheme 11: The Fmoc-glycine loading measurement method used to determine loading of Versabeads^{134,135} a) Fmoc-glycine, 3 equiv; 1-methylimidazole, 6 equiv; 2,4,6-mesitylenesulfonyl-3-nitro-1,2,4-triazolide, 6 equiv; dichloromethane; rt; 1 h, reaction repeated once b) 20% piperidine in dimethyl formamide. UV-measurements performed at 290 nm, and compared to standard.

It was speculated that the attachment of a commercially-available mono-Fmoc protected hexandiamine could be used to determine the loading of chloroformyl linker on resin. However, as this was laborious, results were inconsistent, and the substrate was expensive, it was decided to abandon this method.

Loading of primary and secondary amino groups has frequently been determined through addition of picric acid, followed by release of the salt and UV determination.¹³⁶ An attempt to quantify the tertiary amine in resin-bound 1-diphenylmethylpiperazine by this method gave results in the right order of magnitude, but with too large a spreading. Experiments with resin-bound diethanolamine might have been more beneficial.

4-Nitrophenyl carbamates, which are commonly used in solid-phase synthesis as chlorocarbamate equivalents, form UV active nitrophenolates upon cleavage. This have been exploited previously for loading measurements and reaction monitoring¹³⁷⁻¹³⁹ 4-Nitrophenyl was considered as a cheap alternative to Fmoc-glycine for loading measurements, but the method was not developed due to time constraints.

1.5.5 Elemental analysis

Combustion elemental analysis is one of the few methods available for quantitative determinations of product bound to solid phase.^{19, 140, 141} Unlike the cleave-and-analyse method it has the advantage of not requiring additional steps. Yan *et al.* demonstrated that this method can be used to obtain a very reliable estimate of the yield in the various steps of a solid-phase peptide synthesis.¹⁴¹ This method was used frequently in the project, in order to determine the loading of halogen- and nitrogen-containing species. The only disadvantages with this method were that it does not give any structural information and could not be performed in the laboratory. The method is also of course destructive, but the amounts required are minimal compared to the scale of the reactions.

1.5.6 Atomic Absorption Spectroscopy

Atomic Absorption Spectroscopy (AAS) is a common method for quantitative determination of metals. A liquid sample containing the metal is ionized in an acetylene flame and the metal content is determined by measuring the absorption of the light from an ion-specific hollow cathode lamp.¹⁴² The method has also been used to determine the metal content in resin-bound metal-containing catalysts.^{143, 144}

This method was used in the determination of the loading of metalloporphyrins on resin, and the amount of metal leaching into reaction solution from these. The resin samples were destroyed by heating in concentrated nitric acid, which was filtered and diluted to gain suitable analysis solutions. These were then measured against a standard curve of Mn.

1.5.7 Potentiometric Titration – the Dorman Test

The Dorman test is a method for determining the loading of amino groups on resin by treating the resin with pyridine hydrochloride, followed by neutralization and potentiometric titration with silver nitrate.¹⁴⁵ This was initially considered as an alternative to elemental analysis for halogens, but was not implemented, as a chloride-specific electrode was not readily available, and there was a question as to how to hydrolyze all resin-bound chloride efficiently. It might have been developed as an alternative to elemental analysis, by performing control titration analyses of resin samples of known chloride content.

1.5.8 ¹³C gel-phase NMR

When resin is swollen, the resin-bound species approximate to a solution and are therefore visible in the NMR spectrum. In fact, most known NMR methods can be used to characterize resin-bound species, as demonstrated in a study by the Ley group.¹⁴⁶ ¹³C gel-phase NMR spectroscopy has been used extensively for the monitoring of solid-phase reactions,^{110, 113, 114} often as MAS (magic angle spinning) NMR,^{147, 148} or combined with ¹³C enriched compounds,^{79, 149-151} but often good spectral resolution can be obtained with Standard samples swelled in an NMR tube, and spectrum acquired in a similar manner to standard solution phase samples.^{146, 152,}

¹⁵³ Multiple scans are usually required, and the spectral peaks obtained will be broader than standard in solution due to the differences in relaxation time between inside and outside the resin. Despite this broadening, this analysis method holds the most potential for monitoring the reactions, being sensitive to a multitude of compound functionality, providing structural information, being non-destructive and not requiring other equipment than a standard NMR spectrometer.

¹³C gel-phase NMR was after some initial studies implemented as the method of choice for the monitoring of species on resin. In the beginning of the project only overnight scan methods (13312 scans) were employed, but it was later discovered that a shorter ½ hour method (1024 scans) could often be enough for practical monitoring of reactions. Acquisition times of 7.5 min for certain optimized conditions have been reported.¹⁵²

An especially interesting feature was the ability to estimate the extent of resin loading and cleavage from the resin by means of the ratio of the two carbon peaks closest to the resin's terminal hydroxyl group, which shift very characteristically, depending on whether the group is derivatized or not (Figure 13).

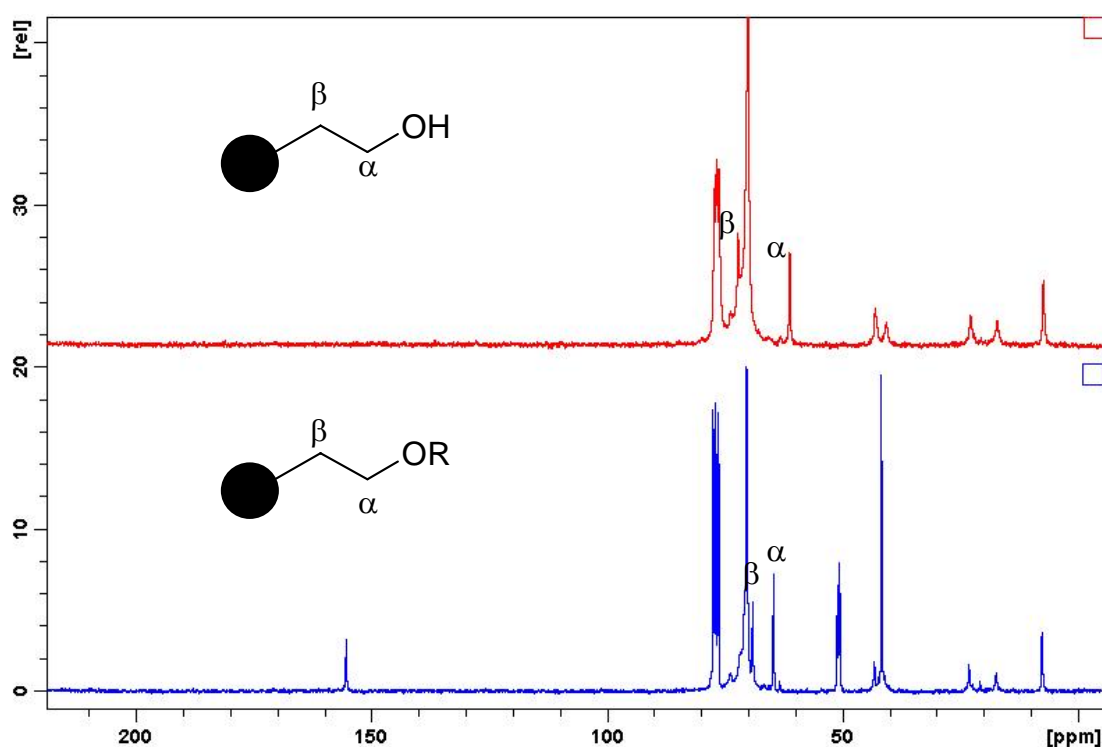


Figure 13: ¹³C gel-phase NMR spectra of Versabeads O 400 (top) and derivatized resin (bottom) in deuteriochloroform. Note the change in position of the carbons α - and β - to the oxygen atom. α moves from 61 ppm to 64 ppm and β from 72 ppm to 69 ppm. In practice the β - carbon peaks will often be obscured by the large framework peak at 70 ppm

1.5.9 ¹H MAS NMR

The gel phase technique cannot be applied to ¹H NMR spectroscopy, due to the short relaxation times of protons, which make the differences in magnetic properties too great for traditional NMR. This can be avoided by spinning the swollen sample in the

“magic angle” ($\theta = 54.7^\circ$), whereby the macroscopic dipolar interactions are averaged out. MAS NMR is today a routine tool in the monitoring of solid-phase reactions in combinatorial chemistry.^{19, 110, 113, 147, 148, 154, 155}

SPOCC – derived resins have shown favourable qualities in ^1H MAS NMR compared to standard Merrifield, due to their flexibility and lack of aromatic groups.^{55, 147, 155} However MAS NMR requires special equipment and trained personnel, and is therefore not as easy to implement as a routine monitoring technique as ^{13}C gel-phase NMR, which can be run with standard NMR equipment.

1.5.10 ^{19}F NMR

NMR active heteronuclei can be used for monitoring the reaction, as the resin framework will not interfere with the NMR spectrum of heteroatoms in gel phase. The most common nucleus to be used in this fashion is ^{19}F ^{19, 110, 156, 157}, but other NMR active nuclei, such as ^{15}N ¹⁵⁸ and ^{31}P ¹⁵⁹ have also been used. The ^{19}F NMR monitoring method does not need to be limited to the solid-phase synthesis of fluorine-containing compounds. For instance it is possible to “tag” a linker with fluorine, thereby obtaining a quick way of monitoring addition and cleavage from the changes in the ^{19}F spectrum.¹⁶⁰⁻¹⁶³ ^{19}F spectroscopy has also been used for optimization work by attaching fluorinated reagents to linker and reagent and then comparing the peaks.⁸¹

In the current project ^{19}F gel phase NMR was used as part of the process to prove the formation of the chloroformyl linker, as well as to identify fluorine- containing species on resin.

1.5.11 FTIR method

FTIR is a much-used method for the investigation of reactions on solid phase as an FTIR spectrum can be obtained very quickly from a single bead. FTIR analysis does not give a clear picture of the compound structure, but it is one of the few methods in solid phase reaction monitoring which can be compared to the standard chromatographic methods used in solution-phase chemistry.^{110, 112, 164-167}

FTIR was measured with the attenuated total reflection (ATR) technique, which allows measurement directly on the dry beads.^{164, 167} FTIR was extensively used in the beginning of the project to monitor attachment and cleavage from the resin judged by the C=O stretch. With the chloroformyl linker the change in absorption from 1776 cm^{-1} to 1701 cm^{-1} could be used to determine if the carbamate was formed, while the difference between the stretch of conjugated and unconjugated ester C=O, from 1724 cm^{-1} to 1734 cm^{-1} was used to monitor addition and cleavage from the REM linker (Figure 14)

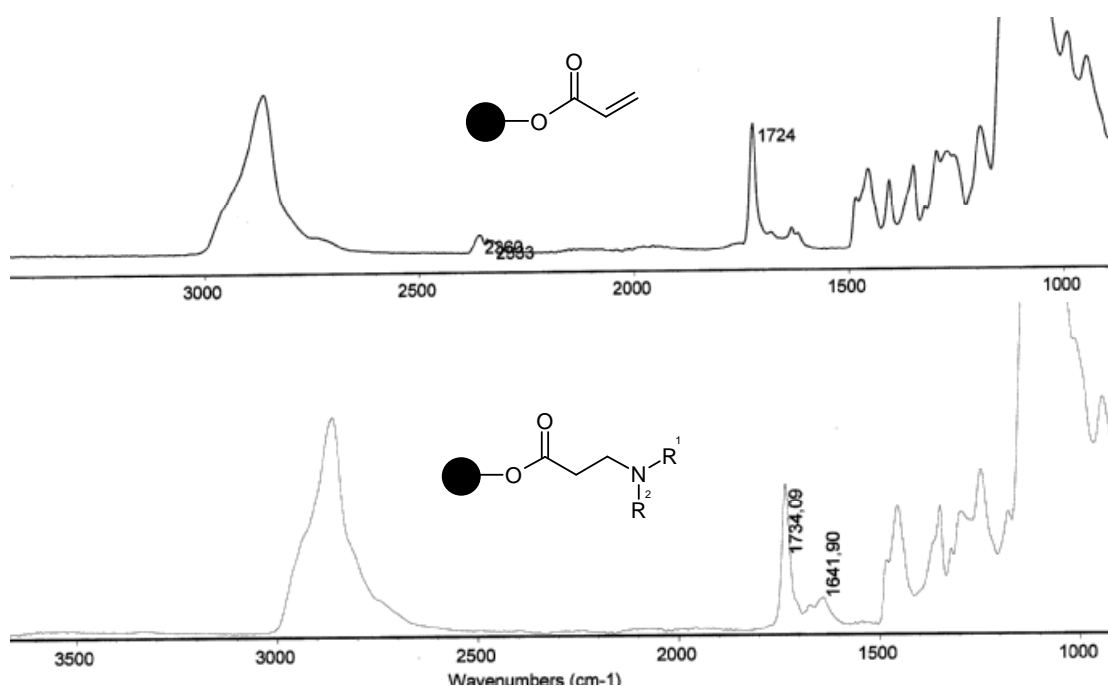


Figure 14: Addition of amine to REM resin causes the C=O stretch to move from 1724 cm^{-1} to 1734 cm^{-1} due to loss of conjugation

The immobilisation and metallation of porphyrins on solid phase was also monitored by the use of FTIR, through the addition and later visible changes in the aromatic stretches.

1.5.12 Near infrared spectroscopy (NIR)

Near infrared spectroscopy (NIR) is often used at H. Lundbeck A/S to investigate the stability of drug formulations. This method has in some cases been used to investigate solid-phase chemistry as well.¹⁶⁸ Attempts were made to use NIR in the current project, but the spectra obtained with the NIR machine at Lundbeck were not sufficiently resolved to provide useful information (Figure 15).¹⁶⁹

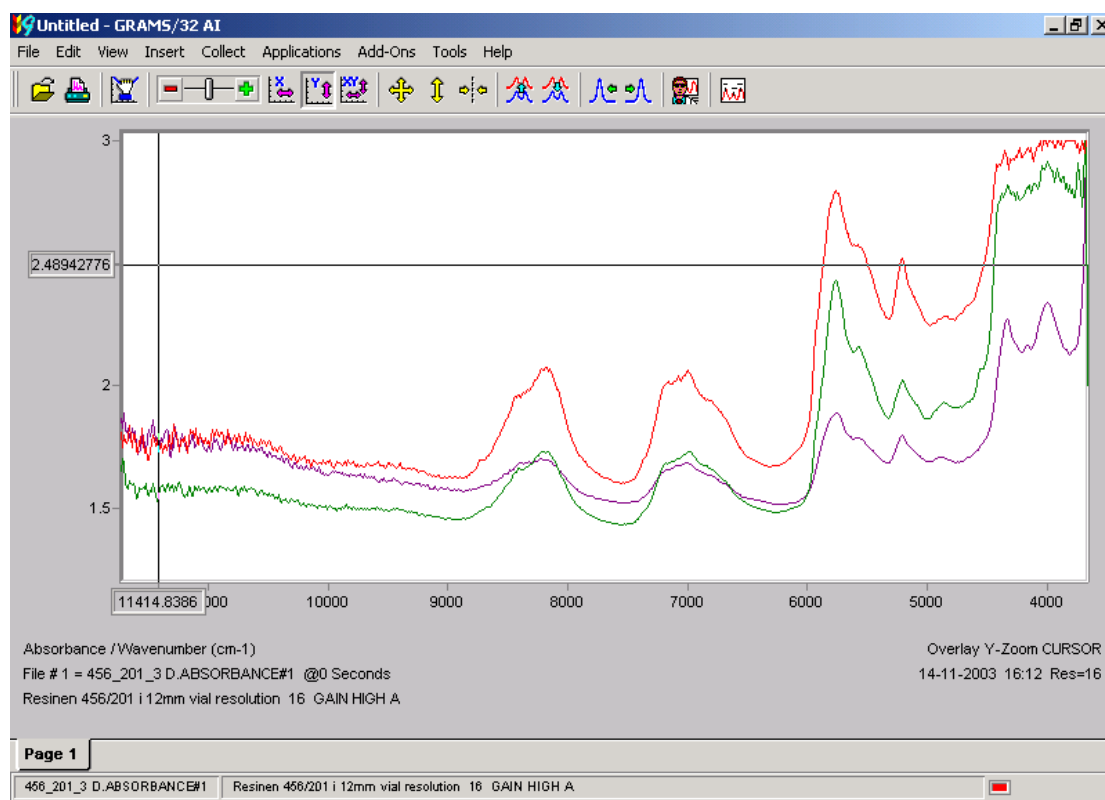


Figure 15: A comparison between the NIR spectra of unfunctionalized Versabeads O400 (purple spectrum) and Versabeads reacted with phosgene (green and red spectrum). The carbonyl group would be expected to appear at approximately $4\text{--}5000\text{ cm}^{-1}$.¹⁶⁹

1.5.13 Other methods – mass spectroscopy

A number of special methods for solid phase reaction analysis based on mass spectrophotometry, such as MALDI-TOF, ion-spray MS and tandem MS have been developed as routine tools for monitoring solid-phase reactions, but these methods are rather specialised and were not considered for the project.^{19, 110}

Raman spectroscopy has been used for reaction monitoring on solid-phase but was not considered for the project, as no convenient probe was available.³²

1.6 Solid-phase synthesis equipment

To avoid loss of resin between steps, solid-phase synthesis is usually performed in fritted reactors. Usually a normal disposable polypropylene syringe, equipped with a frit in the bottom and a valve at the outlet is used as a reactor (Figure 14). Solid-phase synthesis can be performed with normal flasks and filters, but the transfer of solid phase from flask to filter and back can be quite cumbersome. Automated on-line solid-phase synthesizers are available and are used frequently for large-scale synthesis of peptides and other biopolymers.^{25, 27, 28}

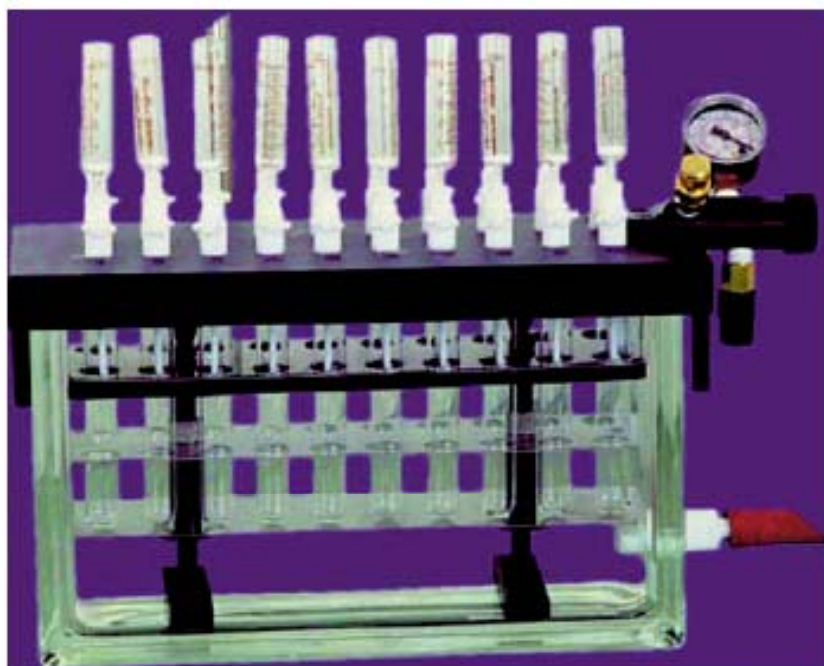


Figure 14: Typical setup for solid-phase reactions. Syringes with fritting and a bottom valve are connected to a form of suction and a reservoir.¹⁴

The resin is suspended in solvent and reagents are added in a manner similar to traditional solution phase synthesis. As most resins are susceptible to mechanical stress and therefore not compatible with magnetic stirring, the preferred agitation method is gentle shaking performed on a shaking board or by fixing the syringe to a wheel

After the reaction has taken place the solvent is removed by suction filtration, and the resin is washed to remove remaining reagents. New reagents are added and a new cycle of react, filter and wash is performed

When the final product is obtained on the resin, it is washed thoroughly to remove all traces of leftover reagent (usually until no reagent is detected in the washes). Cleavage reagents are then added and the filtrate, which now contains the product, is collected. The product is then isolated by traditional workup procedures.¹⁹

If heating is necessary, special Teflon reaction vessels are available, or, for larger scale synthesis, glass reactors, which are larger glass versions of the syringe, with a frit and a valve in the bottom (Figure 5, Figure 6).^{19 31, 32}

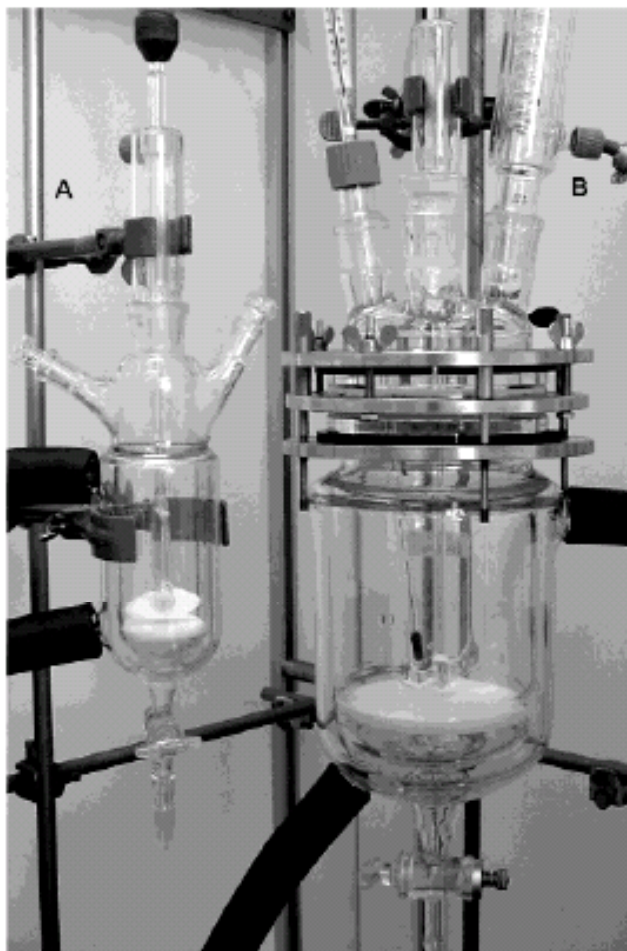


Figure 15: Solid-phase reactors with a volume of 250 mL (A) and 1.5 L (B) used for the work of Meisenbach *et al.* They are equipped with a sintered filter in the bottom and a heat cape for temperature regulation.³²

In the context of this project it was desirable to develop a technique, which employed a minimum of “unusual” equipment, not found in a normal development laboratory. The use of standard round-bottomed flasks and traditional fritted glass Büchner funnels for the filtrations and washings was possible, but cumbersome, and was discovered to be a potential source of loss, as the Versabeads had a tendency to cling to glassware.

The solution to this problem was to employ a thin glass pipe closed in one end with a sinter. This allowed easy wash of the beads directly in their round-bottomed flasks through suction (Figure 16 and 17).

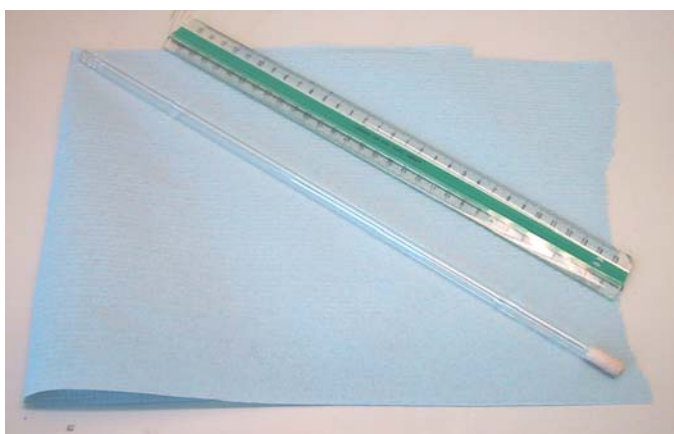


Figure 16: Glass tube with sintered end, used for purification between the steps in larger-scale solid-phase synthesis.



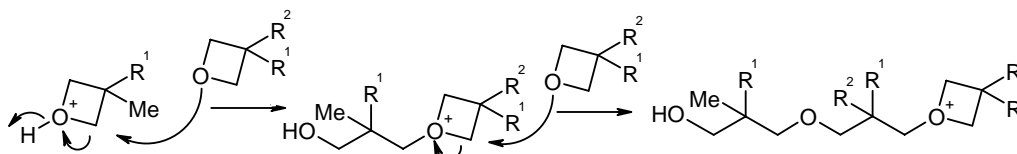
Figure 17: Typical reaction setup for large-scale solid-phase synthesis in the current project. Note the sintered glass tube connected to a reservoir, which allows for easy washing and draining between steps. The tube is removed during reaction.

2 Results and Discussion

2.1 Synthesis of Versabeads

2.1.1 Polymerization theory

Versabeads are synthesised through cationic ring opening polymerization of oxethane-capped macromonomers. When this reaction was developed by Meldal *et al.*, it was the first time cationic polymerization was used in the manufacture of resins for solid-phase synthesis.⁵⁴ It is generally assumed that the ring-opening polymerization of oxethanes proceeds through nucleophilic attack on the α -carbon with simultaneous ring opening (Scheme 12).⁵²



Scheme 12: The polymerization of oxethanes to form Versabeads. Trace amounts of water needs to be present to supply the protons. In this case the polymerization is always initiated on methyl oxethanes, due to steric hindrance.

The resin was made through suspension polymerization, a well-established technique for obtaining beaded polymers of a uniform size. A solution of the hydrophilic monomers and initiator is suspended in a hydrophobic medium (typically silicon or paraffin oil), and aggregates in small droplets, the size of which can be regulated through stirring speed and addition of surfactant.^{52, 170} Suitable hydroxyl functionalization was obtained by copolymerization between mono- and di-dioxetane capped PEG chains (Figure 16).⁵⁴

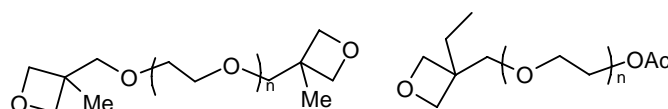
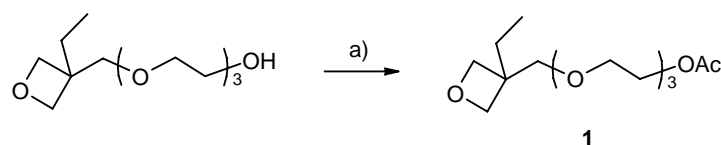


Figure 16: Macromonomers used in the synthesis of SPOCC of the Versabeads type. The length of the PEG chain in the dioxetane monomer is determining for the properties of the resin.

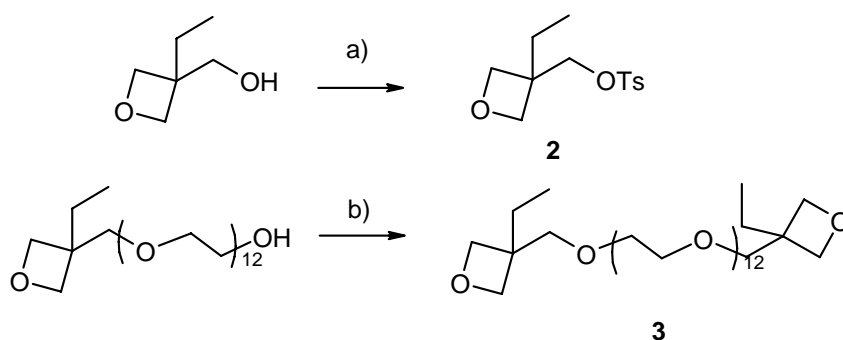
2.1.2 The synthesis of monomers

The two varieties of monomers necessary for producing a SPOCC resin were prepared according to in-house procedures from VersaMatrix A/S from custom-made, oxetane-capped PEGalcohols obtained from Perstorp A/S. Unlike Meldal *et. al.* in their initial experiments, ethyl-substituted oxethanes were used, as they were commercially available.

Two varieties of monomers were used for polymerization. The protected mono oxethane alcohol TOP30 (n=3) was protected with acetic acid anhydride under standard conditions to give monomer **1** in 71% yield (Scheme 13). The alcohol TOP120 (n=12) was capped with the tosylate of 3-(ethyloxethan-3-yl)methanol **2** to give 67 % yield of macromonomer **3** (contaminated with 3% (w/w) *p*-toluenesulphonic acid) (Scheme 13).



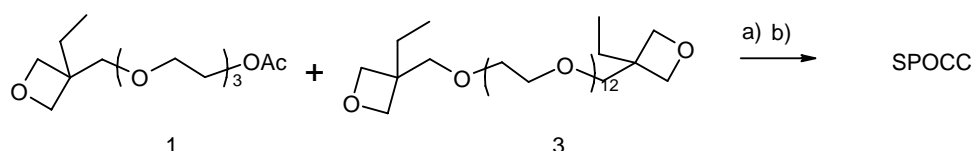
Scheme 13: Synthesis of protected macromonomer (**1**) for SPOCC polymerization. a) Acetic acid anhydride (2.6 equiv), pyridine, r.t., overnight, 71%



Scheme 14: Synthesis of difunctionalized macromonomer (**3**) for SPOCC. a) Tosyl chloride (1.2 equiv), NaOH (1.2 equiv), water/THF, 5°C, 3 h, 64%. b) **2** (1.2 equiv), potassium *tert*-butoxide (1.5 equiv), THF, r.t., overnight.

2.1.3 Polymerization

The polymerization reactions were carried out in a three-necked baffled flask^{34, 170} using a procedure modified slightly from the one described by Meldal *et al.*^{57, 59} A mixture of 44 mol% **1** and 56 mol% **3** was polymerized (Scheme 15)



Scheme 15: Polymerization a) 44 mol% **1**, 56 mol% **3**, Polysurf 30 (1%), BF₃·OEt₂ (0.2 equiv), acetonitrile, Ar atmosphere, -20°C, then silicon oil, 250 rpm, 2 h, r.t., then r.t., overnight. b) Sieving and wash, then 4 M aqueous HCl, 60°C, 2 h.

Sieving of the resin product gave two major fractions, one the desired 120 – 80 μm diameter and one 80-40 μm diameter. Following deacetylation by heating in 4 M aqueous hydrochloric acid the hydroxyl loading of the resin was determined by the Fmoc-glycine method^{135, 171} to be approximately 0.4-0.5 mmol/g (desired loading around 1 mmol/g). At a total yield of 15 g beads this meant a yield of 7.5 mmol hydroxyl groups, a yield of 33% of what was expected. It should be recalled that the polymerization process was still in the optimization phase at this point.

2.1.4 Further work with SPOCC by VersaMatrix A/S

The final Versabeads O products were produced through a different method. Instead of pure ethyl-substituted oxethanes as macromonomers, a mixture of ethyl- and methyl-substituted oxethans were used, as the pure ethyl-substituted oxethane alcohols were found to be less reactive. With a mixture of methyl substituted di-oxethane capped macromonomers and ethyl-substituted mono-oxethane capped macromonomers a relatively uniform chemical structure could be ensured. The disubstituted macromonomers were synthesised from commercially available 3-bromomethyl-3-methyloxethane and PEG of various chain length. Finally silicon oil was substituted by paraffin oil as polymerization medium out of economic concerns.⁵⁸⁻⁶⁰ As the physical and chemical properties of the resins were not found to depend significantly upon the synthesis pathway, the specific methods of resin synthesis and the type of starting material (methyl or ethyl monomers) have not been noted in the experimental.

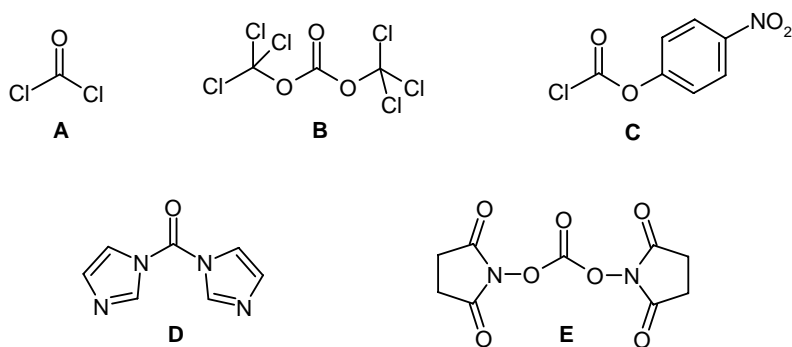
2.2 Linker synthesis

It was initially decided to investigate the carbamate linker and REM linker as linkers for amino functionalities on SPOCC resin, as they were deemed the most amenable for scale-up and reuse.

2.2.1 Carbamate linker synthesis

2.2.1.1 Synthesis methods

The carbamate linker is most commonly prepared by reacting phosgene or a phosgene equivalent with a hydroxyl group on the resin, and thereafter with an amine. Various starting materials are available for this transformation (Table 3).



| Entry | Compound | Available quantities | Equivalents (mmol) | Price (€) | Price/equivalent (€/mmol) |
|-------|----------|----------------------|--------------------|-----------|---------------------------|
| 1 | A | 500 mL | 945 | 145.3 | 0.15 |
| 2 | B | 10 g | 101 ^a | 44.4 | 0.44 |
| | | 50 g | 505 ^a | 164.3 | 0.32 |
| 3 | C | 10 g | 50 | 38.6 | 0.77 |
| | | 50 g | 250 | 138 | 0.55 |
| | | 250 g | 1250 | 555 | 0.44 |
| 4 | D | 25 g | 154 | 46.6 | 0.30 |
| | | 100 g | 617 | 154.6 | 0.25 |
| 5 | E | 5 g | 20 | 55.7 | 2.8 |
| | | 25 g | 100 | 217.2 | 2.2 |

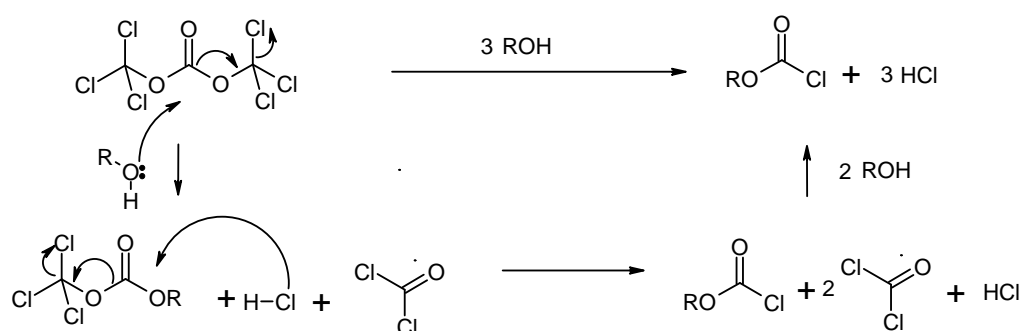
Table 3: Comparison of prices for phosgene and various phosgene equivalents. (after FLUKA, 2004-05) ^a1 mmol of **B** = 3 mmol of **A**.

2.2.1.1.1 Phosgene

Phosgene (Table 3, compound A) is the cheapest and simplest reagent for the synthesis of a carbamate linker, and has been frequently employed for this purpose, usually as a solution in toluene.¹⁷²⁻¹⁷⁶ No additional base is needed. Phosgene is very toxic and volatile, and although the commercially available 20 % (w/w) toluene solution is fairly safe to handle in an efficient hood, some alternative form is preferable for use on larger scale.

2.2.1.1.2 Bis(trichloromethyl) carbonate (triphosgene)

Bis(trichloromethyl)carbonate (Table 3, compound B), also known as BTC or triphosgene, is a white crystalline solid which is obtained by the extensive chlorination of dimethyl carbonate.^{174, 177, 178} When exposed to base or heat it decomposes slowly to form 3 equivalents of phosgene.¹⁷⁹⁻¹⁸¹



Scheme 16: Decomposition of triphosgene¹⁷⁸

Triphosgene still develops the very-toxic phosgene, but it is markedly easier to control than the gaseous phosgene, and have been frequently used as a phosgene source, also on large scale.¹⁸² It has also been employed for the generation of solid- and solution-phase carbamate linkers in several instances^{176, 183, 184}

2.2.1.1.3 *p*-Nitrophenyl chloroformate

p-Nitrophenyl chloroformate (Table 3, compound C) is a popular and safe phosgene substitute for linking amines to solid phase *via* the carbamate linker.^{68, 137, 185-191} It has the added advantage of being easier to detect on resin, as it is clearly visible and distinct in the NMR spectrum. *p*-Nitrophenol is strongly coloured and the reagent has been used as a quantification agent for hydrophilic polymer similar to Fmoc glycine.¹³⁷ Compared to phosgene and triphosgene it has the disadvantages of being more expensive and, as the *p*-nitrophenol ring is lost during carbamate formation, less atom economic as well.

2.2.1.1.4 Other phosgene equivalents

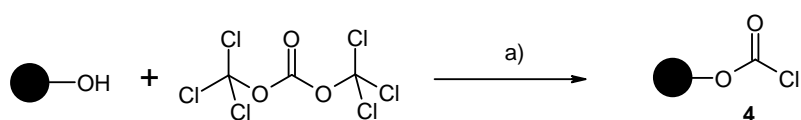
Carbonyl diimidazole (Table 3, compound D) is cheaper pr. mol than 4-nitrophenyl chloroformate, and has previously been used to generate a carbamate linker,^{173, 192, 193} but it loses two imidazole molecules in the process and was therefore rejected as not atom economic.

Di-*N*-succinimidyl carbonate¹⁹⁴ (Table 3, compound E) has been used to generate carbamate linkers, but it is both more expensive and less atom economic than the alternatives.

Salvatore *et. al.* used carbon dioxide in combination with amines to generate carbamate linkers in one step¹⁹⁵. This has the potential to be a good route to the carbamate linker, as it uses only non-toxic reagents and saves a step. However, the method was deemed to be too complicated to develop given the limited timeframe of the project.

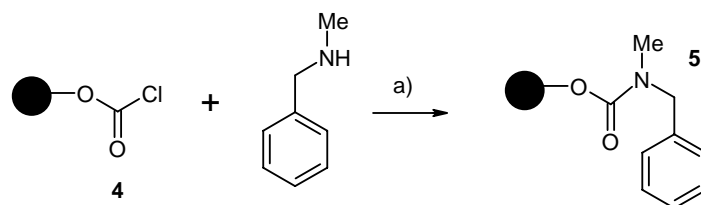
2.2.2 Synthesis and proof of concept.

Triphosgene was initially chosen as the starting material for the generation of the linker, and was reacted with the freshly-prepared resin using pyridine as a base¹⁹⁶ to give chloroformyl resin **4** (Scheme 17).



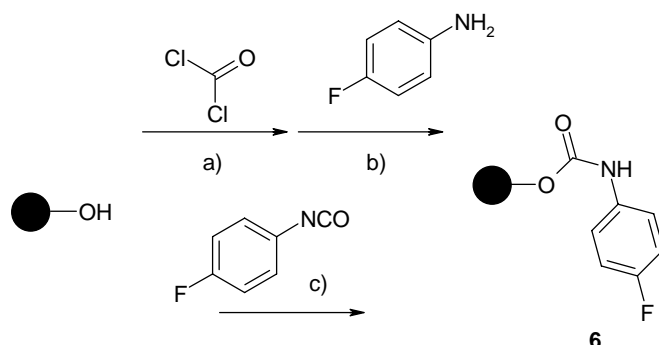
Scheme 17: Initial synthesis of chloroformate linker **4**. a) triphosgene (8 equiv), pyridine (2.5 equiv), DCM, r.t., overnight.

The chloroformyl group was easy to identify in the resin FTIR spectrum as a sharp peak at 1771 cm^{-1} ,¹⁷³ and elemental analysis for Cl yielded a loading of 0.3 mmol/g. The linker was not visible in ^1H MAS NMR and ^{13}C gel-phase NMR, but later attachment of *N*-methyl-*N*-benzyl amine¹⁷⁵ (**5**) showed a change in the IR spectrum, where the carbonylic stretch had moved to 1705 cm^{-1} as expected (Scheme 18).



Scheme 18: Making a derivative of the chloroformate linker as proof of concept. a) *N*-benzyl-*N*-methylamine (17 equiv), DIPEA (4 equiv), DMF, r.t., overnight.

Final proof of concept was achieved by reacting 4-fluoroaniline with chloroformylated resin and hydroxyl resin with 4-fluorophenyl isocyanate¹⁹⁷, and comparing the ¹³C and ¹⁹F NMR spectra of the two products (**6**), which were found to be identical (Scheme 19)



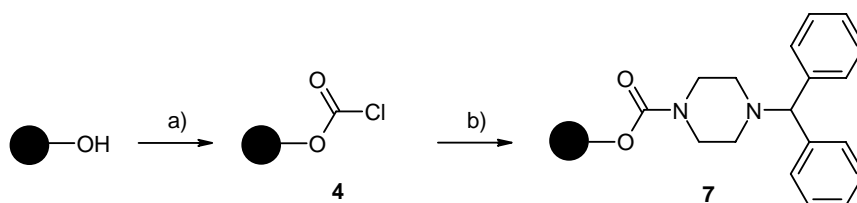
Scheme 19: Proof of concept for the chloroformyl linker **4**. a) phosgene (20% (w/w) in toluene, 9 equiv), THF, r.t., overnight. b) 4-fluoroaniline (24 equiv), 6 h, THF, r.t., 6 h. c) 4-fluorophenyl isocyanate (13 equiv), triethylamine (cat.), DCM, r.t., 20 h.

In this synthesis the linker was made using phosgene in toluene as the starting material. It was not entirely sure which starting material was better, as a proper yield could not be established until a suitable cleaving reaction was found.

2.2.2.1 Cleavage of the carbamate linker

To investigate the properties of the new linker, 1-diphenylmethylpiperazine was chosen as a standard compound for attach and cleavage tests, because of its good UV absorbing qualities and characteristic aromatic proton NMR spectrum.

Attachment of amines to the carbamate linker to form compound **7** seemed to proceed without difficulty, using the same conditions as Hauske and Dorff (excess amine and non-nucleophilic base) as judged by IR and CHN ¹⁷³ (Scheme 20)

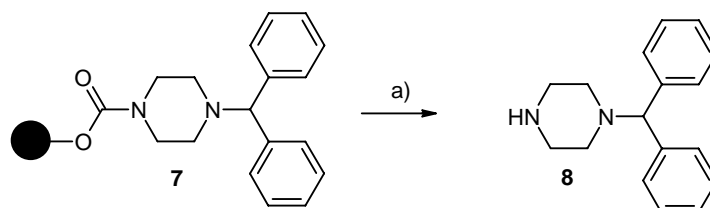


Scheme 20: Attachment of test compound a) Phosgene (20% (w/w) in toluene, 5 equiv), THF, r.t., 7 h OR triphosgene (5 equiv), pyridine (5 equiv), THF, r.t. 7 h. b) 1-dimethylphenylpiperazine (5 equiv), triethylamine (5 equiv), THF, r.t., overnight.

Cleavage of the linker proved more difficult. Initial experiments with the standard cleavage method for carbamate – Wang linker (50% trifluoroacetic acid in DCM)

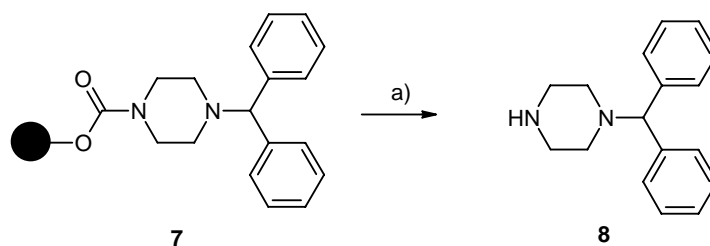
showed that this linker was stable under the conditions (Table 4, entry 1). This was not surprising, as methyl- and ethyl carbamate protection groups in solution are cleaved under much more forcing conditions than benzylic carbamates.⁶² Experiments with more forcing conditions and microwave heating revealed that quite forcing conditions were needed to cleave the linker (Table 4).

The beads gained a brown colour, but later investigation by microscope and IR revealed that they did not appear to be damaged. In an attempt to find milder cleavage conditions a series of experiments were performed with mineral base in alcohol and microwave heating (Table 5).



| Entry | Conditions | Result | Yield ^a | Reference: |
|-------|----------------------------------------------------------------------------------|----------------------------|--------------------|------------|
| 1 | trifluoroacetic acid/DCM (1.5:1), r.t. 1h, repeated | N analysis 1.1% | - | 198 |
| 2 | Concentrated aqueous HBr(48%)/acetic acid (1:1), r.t., overnight | N analysis 2.4% | - | 199 |
| 3 | LiOH (1.5 mmol, 20 equiv) water/ethanol (1:2), 80°C, 1.5 h ^b | N analysis 2.4% | <5 % | 200 |
| 4 | Concentrated aqueous HBr(48%)/acetic acid (1:1), 80°C, 1.5 h ^b | N analysis 2.2 % | <5 % | 199 |
| 5 | trifluoroacetic acid/DCM (1.5:1), 80°C, 1.5 h ^b | N analysis 2.4 % | decomposed | 198 |
| 6 | NH ₃ (4M in methanol), r.t., overnight, then 60 °C/1.5 h ^b | IR = 1701 cm ⁻¹ | none | 201 |
| 7 | KOH (5 equiv)/ethanol 150 °C/2 h ^b | No carbamate stretch in IR | 42 % ^c | 202 |

Table 4: Initial attempts to cleave the carbamate linker. ^aYield estimated from ELSD spectrum. Method gave lower results than the actual (test gave 73% of actual compound content). ^bHeated with microwaves in closed Process Vials on an Emrys Optimizer ^cIsolated crude yield (estimated from weight and ¹H NMR purity)



| Entry | Reagent /equiv | Solvent | Conditions | IR (cm ⁻¹) | Yield 8 (ELSD) ^a |
|-------|--------------------|-----------------------|---------------|------------------------|------------------------------------|
| 1 | KOH/ 1.5 equiv | ethanol/ 6% water | 150°C, 30 min | 1702 | 16% ^b |
| 2 | LiOH/ 1.5 equiv | ethanol/ 6% water | 150°C, 30 min | 1701 | 16% ^b |
| 3 | NaOH/ 1.5 equiv | ethanol/ 6% water | 150°C, 30 min | 1701 | 16% ^b |
| 4 | LiOH/1.5 equiv | methanol/ 6% water | 150°C, 30 min | 1702 | 41% |
| 5 | LiOH/1.5 equiv | methanol/ 6% water | 150°C, 60 min | 1702 | 41% |
| 6 | HBr/ 5 equiv | methanol/water | 150°C, 30 min | 1705 | none |
| 7 | KOH/ 5 equiv | methanol/water | 150°C, 30 min | 1701 | 45% |
| 8 | LiOH/ 5 equiv | methanol | 150°C, 1.5 h | 1701 | 58% |
| 9 | KOH/ 5 equiv | methanol | 150°C, 1 h | no | 58% |

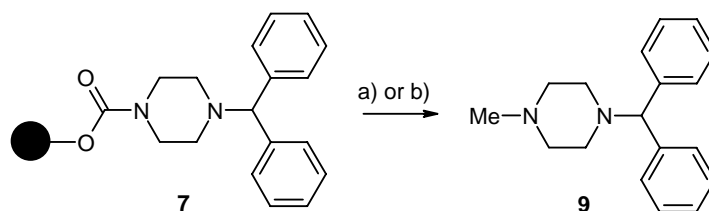
Table 5: Selected results from the screening of cleavage conditions with microwave heating ^aEstimated from ELSD spectrum. Method gave lower results than the actual (test gave 73% of actual compound content) ^bThese reactions yielded an approx. equal (by ELSD) amount of the *N*-ethyl carbamate of **8**.

Unfortunately yields from these screening reactions were uniformly low, and IR spectra of the resins still showed a carbamate stretch after reaction. Only prolonged heating with methanolic potassium hydroxide seemed to cleave the linker completely (Table 5, entry 9). It was decided to temporarily abandon these efforts and examine cleavage under reductive conditions instead.

2.2.2.2 Reductive cleavage

As previously mentioned Wang carbamate linker can be cleaved with Lithium aluminium hydride to yield methyl amines.^{68, 203} This reagent tends to form large excesses of solid aluminium salts, which can be problematic to separate from the product, especially in a solid-phase synthesis where prolonged washing procedures are employed. It was therefore decided initially to use lithium borohydride as a cleaving agent instead, after a standard procedure in THF containing 1 equivalent of methanol.²⁰⁴

To determine both the feasibility of this cleavage method and to compare the triphosgene-based method with the phosgene-based method, two chloroformylated resins were prepared, one using triphosgene and pyridine, one using phosgene in toluene. Both were reacted with a solution of 1-diphenylmethylpiperazine in THF under the same conditions, and both were then cleaved using the same conditions: 10 equivalents of lithium borohydride in THF (Scheme 21, a))



Scheme 21: Reductive cleavage of the test compound. a) LiBH_4 (10 equiv), methanol (10 equiv), THF, reflux, overnight b) LiAlH_4 (10 equiv), THF, reflux overnight.

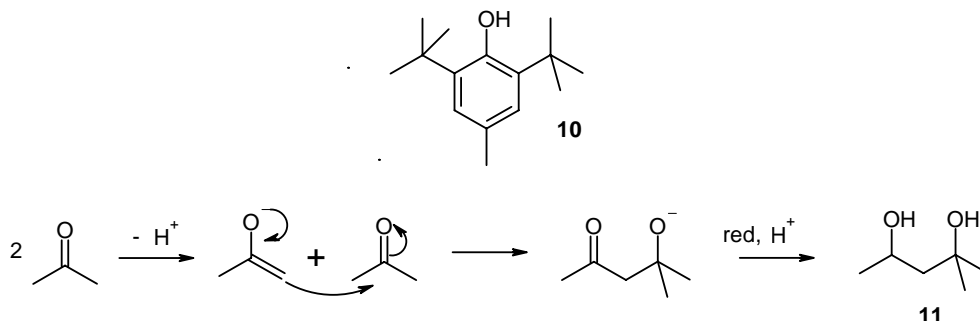
The product was completely cleaved from the resins, as judged by the disappearance of the carbonyl stretch in the IR spectrum.

In both products a significant amount of the secondary amine resulting from nucleophilic cleavage was present (~20%), and both reaction products contained a small amount of impurity in the form of a yellow oil.

The crude yield from the phosgene-functionalized resin was significantly larger than the yield from the triphosgene-functionalised resin, so the phosgene-functionalised resin was chosen for further reactions.

The yellow oil impurity appeared in all reactions cleaved with this method. Treatment of 12.2 g of non-functionalized Versabeads with lithium borohydride-methanol in THF after the same method yielded 400 mg of the impurity. The NMR spectrum of this material showed a mixture of aliphatic and aromatic protons, and as it had a similar mass spectrum as vacuum grease and contained aliphatic protons similar to the paraffin oil used for polymerization, it was initially believed to be an impurity from

the resin production process, but the Versabeads treated with reductive conditions had not lost weight proportional to the impurity formed. Upon closer examination the yellow oil was discovered to be a mixture of stabilizer from the THF (**10**) and the compound 2-methyl-2,4-pentandiol (**11**), the latter in all likelihood formed during the quench of the reduction using acetone.²⁰⁵



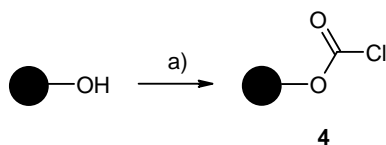
Scheme 22: By-products from the LiBH_4 – methanol reductive cleavage method: THF-stabilizer (**10**), and side-product from acetone quench (**11**).

Changing the quench reagent to ethyl acetate, and a wash of the acidic water phase during workup removes both impurities from the final product.

The presence of the secondary amine upon cleavage with lithium borohydride persisted, and cutting down the use of reduction agent to only 5 equivalents of reducing agent did not yield complete cleavage from resin. The comparison between cleavage with 10 equivalents of solid lithium borohydride and 10 equivalents of solid lithium aluminium hydride with the same reaction times revealed that nucleophilic cleavage did not occur when lithium aluminium hydride was used. It was therefore decided to use lithium aluminium hydride as the cleavage agent. This reagent was quenched with water and the by-product **11** was therefore not formed. The THF stabilizer **10** was removed through wash of the acidic aqueous phase with ethyl acetate.

2.2.2.3 Optimization of linker formation

To determine optimum conditions for the synthesis of the carbamate linker a series of experiments with various reaction times and equivalents of phosgene was performed. It was discovered that two equivalents of phosgene for 2 hours was enough to ensure full loading of the resin (Table 6). The $> 100\%$ yield is calculated based on the loading measured through the Fmoc- glycine method. It is believed that the small phosgene molecule is able to react with those less accessible hydroxy functionalities on the resin that the large Fmoc- glycine molecule cannot reach.



| Entry | equiv phosgene | time (h) | IR (cm ⁻¹) | Cl (%) | loading (mmol/g) | Yield |
|-------|-------------------|----------|----------------------------|-----------|---------------------|-------|
| 1 | 2 | 4 | 1775 | 6.93/6.96 | 2.0 | 118% |
| 2 | 2 | 2 | 1775 | 6.46/6.44 | 1.8 | 106% |
| 3 | 5 | 2 | 1774 | 7.27/7.34 | 2.1 | 121% |
| 4 | 2 | 6 | 1775; 1743 ^a | 5.53/5.45 | 1.6 | 91% |
| 5 | 5 | 6 | 1776; 1749 ^a | 7.12/7.05 | 2.0 | 118% |

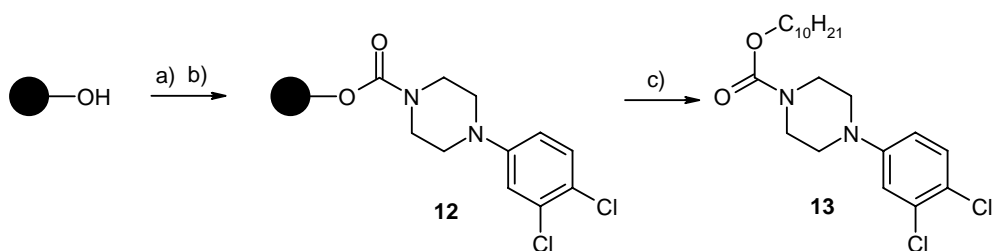
Table 6: Screening for optimised conditions for the generation of the chloroformyl linker **4**. a) Phosgene in toluene (20% w/w), THF, r.t. ^aPossibly cross-linking between sites.

2.2.2.4 Nucleophilic- and base-mediated cleavage revisited

The initial experiments with nucleophilic cleavage under microwave heating had revealed that forcing conditions were needed to cleave the carbamate linker. When conventional heating was applied to a suspension of a resin-bound piperazine with 10 equivalents of potassium hydroxide in methanol the linker was completely cleaved upon reflux. The product hereby generated was the methyl carbamate of the amine in question (see scheme 35).

This prompted a more thorough investigation of base-mediated cleavage, and it was found that cleavage using potassium tert-butoxide yielded complete cleavage upon reflux with 2 equivalents in diethylene glycol dimethyl ether (DME), probably due to the presence of trace amounts of water.

When methanol-wet resin was employed in the cleavage reaction the methyl carbamate was formed, in some cases as the only product. Similar nucleophilic cleavage to yield additional functionalization is known,^{183, 184, 189, 206} and a cleavage protocol based on this could potentially expand the scope of this linker greatly. Experiments with adding 10 equivalents of a higher aliphatic alcohol (decanol) to the cleavage reaction did, however, not lead to the formation of carbamate **13** in solution (Scheme 23), and further experiments in this field were abandoned due to time constraints.



Scheme 23: a) phosgene (20% w/w in toluene, 2 equiv), THF, r.t., 2 h. b) 1-(3,4-dichlorophenyl)-piperazine (2.5 equiv), triethylamine (5 equiv), THF, r.t., overnight. c) 1-decanol (5 equiv), potassium *tert*-butoxide (5 equiv), DME, reflux, 5 h. No yield.

Attempts to cleave the carbamate linker with potassium hydroxide in water did not yield promising results.

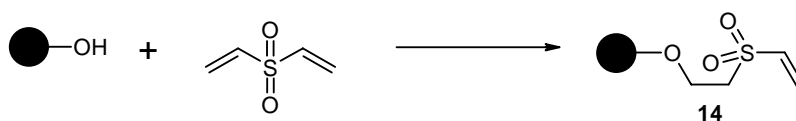
2.2.3 The synthesis of various REM linkers

The REM linker concept has several advantages in the context of amine synthesis on a larger scale on Versabeads. Both the attachment reaction and the cleavage reaction have been shown to be enhanced by aqueous media, meaning that it is an ideal showcase for the advantages of having the compound immobilized on a hydrophilic resin.

2.2.3.1 Sulfone-based REM linker

Heinonen *et al* produced their sulfone-based REM linker in one step from divinyl sulfone by reaction with a Wang linker *via* a Michael reaction using a catalytic amount of DBU as base.^{99, 100, 207} When this was attempted on SPOCC to synthesise the linker **14** no addition was observed by IR, but elemental analysis showed sulfur content corresponding to ca. 40 % loading, and possible vinylic protons were seen in the ¹H MAS NMR spectrum (Table 7, entry 1). An attempt was made to add *N*-benzyl-*N*-methylamine to the resin⁹⁷ but as this did not yield any changes in the NMR spectrum it was concluded that the handle had not been made, and that the sulfur found in the elemental analysis had to come from another source, possibly polymerized divinyl sulfone left inside the resin.

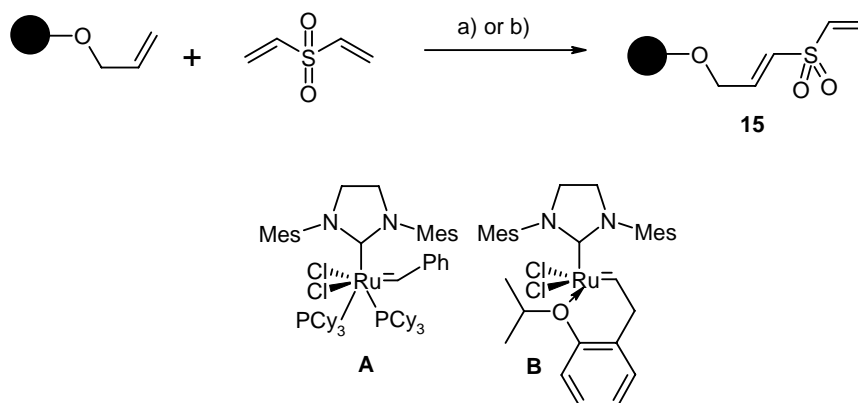
Attempts to form this linker using divinyl sulphone and other reagents such as Triton B^{102, 208} (table 7, entry 2) or NaOH²⁰⁹ (table 7, entry 3) did not produce any changes in the IR spectrum, and again no changes in the spectrum were seen upon addition of nucleophiles. The resin was probably not sufficiently nucleophilic to add to the sulphone. An attempt to activate the resin using *tert*-butoxide as a base resulted in polymerization of the divinyl sulphone.



| Entry | Equivalents divinyl sulphone | Base | Conditions | Reference |
|-------|------------------------------|-----------------------|-----------------------------------|-----------|
| 1 | 12 | DBU | 1 equiv, DCM, r.t. overnight | 99 |
| 2 | 1.5 | Triton B ^a | catalytic base, DCM, r.t., 4 days | 208 |
| 3 | 9 | NaOH | 0.35 equiv, THF, r.t., 3 days | 209 |

Table 7: Attempted synthesis of a sulfone REM linker in one step from divinyl sulfone. ^aTriton B: a 40 % aqueous solution of *N*-benzyl-*N*- trimethylammonium hydroxide.

VersaMatrix A/S also produces Versabeads functionalized with an allyl ether moiety. As it is known that divinyl sulphone can undergo cross-methathesis reactions with the second generation Grubbs carbene catalyst (**A**, scheme 24), and cross metathesis on resin is known,^{210, 211} it was decided to try this approach in order to form the vinyl sulphone linker **15**. Resin, flask and solvent were carefully dried and degassed prior to reaction, but IR and elemental analysis detected no sulphone linker on the resin after the reaction. An attempt to synthesise the linker using the more stable second-generation Hoveyda carbene (**B**, Scheme 24)²¹² as catalyst proved to be unsuccessful as well.



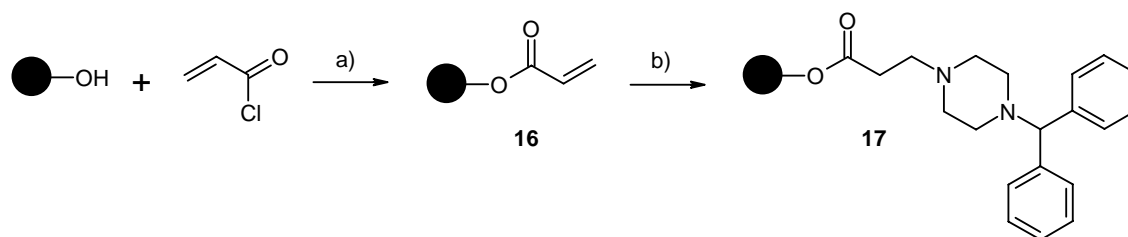
Scheme 24: Attempted synthesis of a sulfone REM linker (**15**) through methathesis. a) divinyl sulfone (2 equiv), **A** (0.1 equiv), DCM, reflux, overnight. b) divinyl sulfone (6 equiv), **B** (0.1 equiv), DCM, reflux, overnight. (Mes- = 2, 4, 6 – trimethylphenyl-)

The resin had gained a greyish colour after reaction, and it was speculated whether the lack of success with the metathesis reaction was due to the crown-ether like structure of the resin trapping the metal. Recently however, Grubbs *et al* has demonstrated the immobilization of an analogue of **A** on PEG and its utility in aqueous reactions,²¹³ and although the flexible PEG chain cannot entirely be compared to SPOCC, this indicates that the catalyst should be stable under the conditions. The problem is therefore rather one of reactivity. Breed, Ramsden and Brown notes that solid-phase cross metathesis reactions are difficult to get to run to completion.²¹⁴

It was decided to investigate using acrylates as a linker instead, as the synthetic procedures for making ester bonds are better established than the ones for addition of divinyl sulphone to resin.

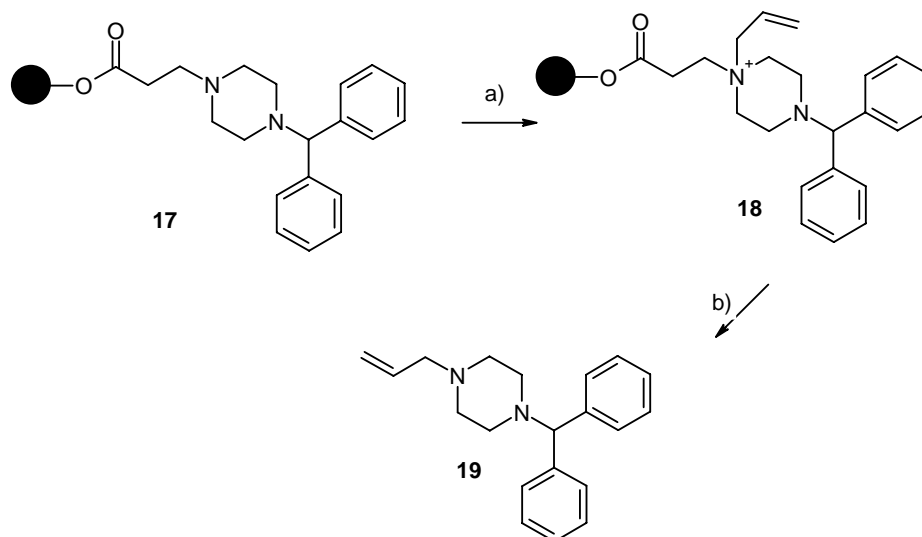
2.2.3.2 Acrylic acid-based REM linker

The acrylic acid handle **15** was formed through the procedure developed by Morphy *et al.*⁷⁹ The linker synthesis proceeded to completion judged by ¹³C gel-phase NMR and it was decided to test it with the same reactions as used in the original reference, where 1-diphenylmethylpiperazine was used as a test compound (Scheme 25)



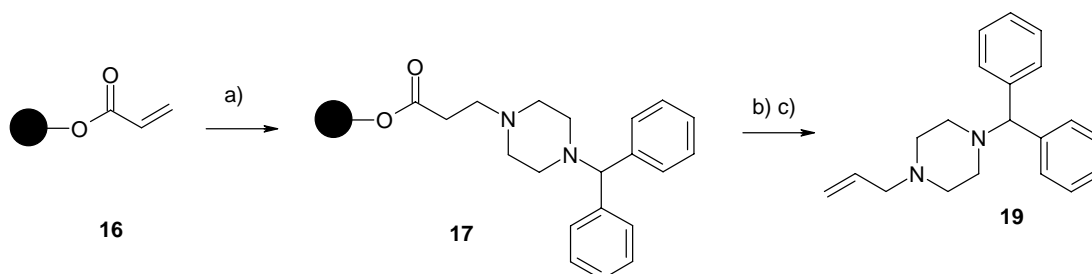
Scheme 25: Synthesis of the REM linker **16** and subsequent derivatization a) Acryloyl chloride (10 equiv), DIPEA (10 equiv), DCM, r.t., overnight. b) 1-diphenylmethylpiperazine (5 equiv), THF or DMF, r.t., overnight

The Michael addition of 1-diphenylmethyl piperazine to **16** to form resin **17** proceeded to completion according to ¹³C gel-phase NMR. The following reaction between **17** and allyl bromide in water did not give complete reaction, judged by ¹³C gel-phase NMR. The final crude yield of **19** after basic cleavage was 32 % (Scheme 26).



Scheme 26: Reaction with allyl bromide, followed by cleavage a) allyl bromide (5 equiv), water, r.t., 6.5 h, repeated overnight. b) DIPEA (2 equiv), DCM, r.t. 5 h. Crude yield 32%

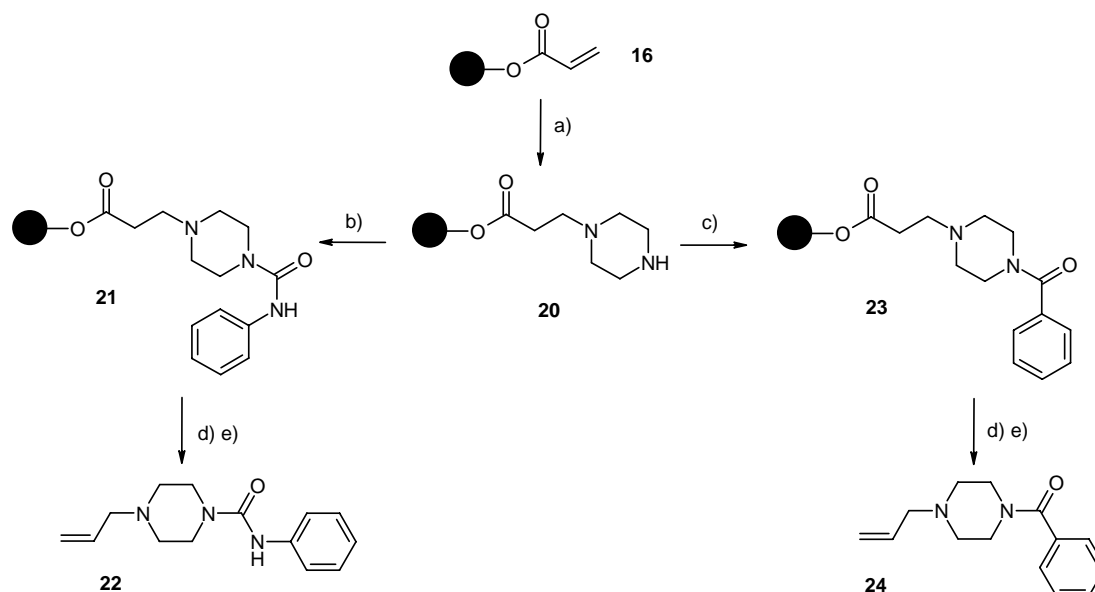
A small-scale experiment where the test reaction was assisted by microwave heating gave a promising result of 19% yield of 1-allyl-4-diphenylmethylpiperazine and complete cleavage from resin by ^{13}C gel-phase NMR, as indicated by the presence of acrylic carbon. A later experiment with microwave heating gave a yield of 40 % overall yield of **19** (Scheme 27).



Scheme 27: a) 1-diphenylmethylpiperazine (5 equiv), THF, 60°C, microwave, 1 h. b) allyl bromide (5 equiv), water, 60°C, microwave, r.t., 1h. c) DIPEA (2.2 equiv), DCM, 60°C, microwave, 45 min. Yield: 40%

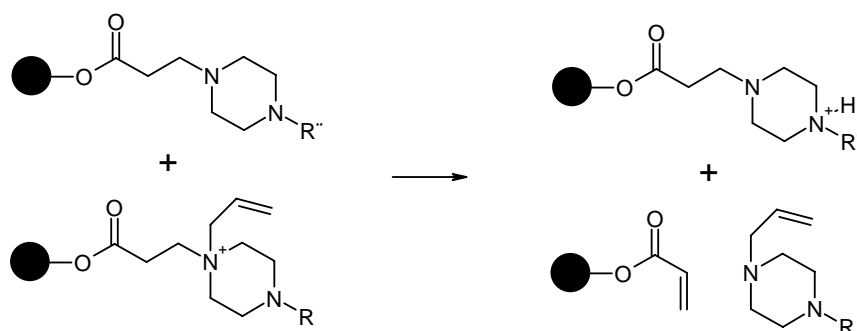
As large-scale microwave chemistry is still in its infancy this route was not further explored, but it holds potential in future combinatorial uses of REM.

Morphy *et al.* attached piperazine to the REM linker and was able to synthesise allyl piperazine derivatives with different *N*-substituents from this. When these reactions were performed on Versabeads, the expected products were isolated in reasonable crude yields (Scheme 28).



Scheme 28: Synthesis of substituted piperazines on REM resin. a) piperazine (12 equiv), DMF, r.t., overnight. b) phenyl isocyanate (10 equiv), DMF, r.t., overnight. c) benzoyl chloride (2 equiv), triethylamine (2 equiv), DCM, r.t., overnight. d) allyl bromide (5-6 equiv), water, r.t., overnight. e) DIPEA (3-4 equiv), DCM, r.t. 6-7 h. Crude yield **22** (35%) **24** (38%)

It was known from Morphy *et al* that interaction between basic centres on resin could lead to premature cleavage in the quaternization step⁸¹ (Scheme 29). Compound was detected by LC/MS in the washing from many of the synthesis.



Scheme 29: Proposed intra-resin premature cleavage mechanism.⁸¹

When the test reaction was scaled up to gram scale on high loading resin (1.6 mmol/g), yield of **17** were low, and significant cleavage was again seen in the quaternization step. This made it clear that the REM linker protocol was promising, but required much effort if it was to be developed for large-scale synthesis. The problem with insufficient quaternization and premature cleavage needed to be addressed, and new conditions for the attachment of compound, using fewer equivalents of compound and non-carcinogenic solvents had to be developed.

As the carbamate linker protocol was at this point much closer to a scalable synthesis route it was decided to concentrate the efforts on this linker.

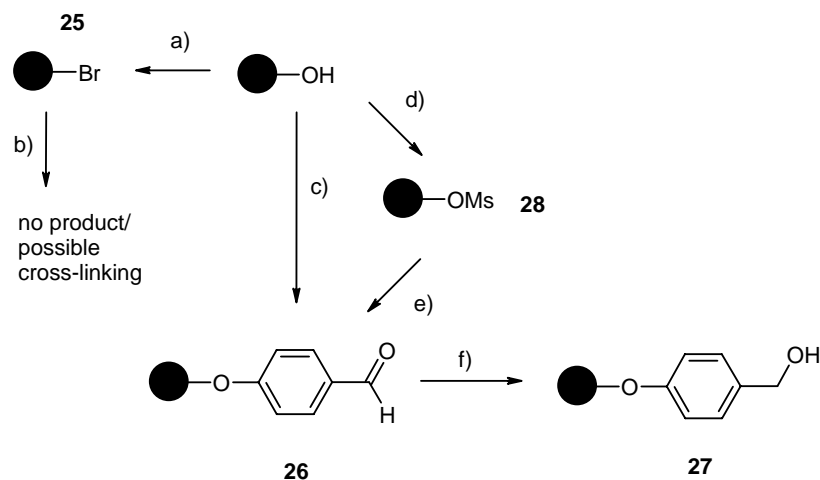
2.2.4 Wang linker

As previously mentioned, the majority of uses of a carbamate linker in literature are in conjunction with a Wang linker in order to facilitate cleavage. When it was observed in our case that very harsh conditions were required to cleave the carbamate linker from Versabeads, an attempt was made to attach a Wang linker to the resin. Two methods were investigated: nucleophilic addition and a Mitsunobu route (Scheme 30).

The resin was functionalized using a procedure developed by Meldal *et al.* via triphenylphosphine-assisted substitution of hydroxide with bromide.⁵⁴ ¹³C Gel phase NMR indicated complete reaction (*i.e.* only brominated product was observed), but elemental analysis indicated a loading of only approximately 30% of theoretical maximum. An attempted bromide substitution by 4-hydroxybenzylalcohol did not yield the desired Wang linker, as judged by ¹³C gel-phase NMR. It appears that the main reaction has been some sort of cross-linking, as no peaks from -CH₂OH is visible in any of the spectra, although Br- loading of **25** was low.

Reaction between Versabeads and 4-hydroxybenzaldehyde under Mitsunobu conditions yielded almost complete functionalisation by ¹³C gel-phase NMR.²¹⁵ The resin-bound aldehyde **26** was then reduced to the alcohol using sodium borohydride to give Wang linker **27**.³¹ Conversion was complete judged by ¹³C gel-phase NMR (Scheme 30). Later experiments demonstrated that mesylation of the resin followed by nucleophilic addition was another efficient way to immobilize hydroxybenzyl aldehyde on resin (Scheme 30).⁶³

Further experiments with Wang linkers were abandoned when the reductive cleavage of the carbamate linker from the resin was developed, as this required fewer steps from Versabeads to synthesis product. Wang-functionalized Versabeads were later commercialized by VersaMatrix A/S.⁶⁰



Scheme 30: Synthesis of Wang linker on Versabeads. a) Br₂ (5 equiv), triphenylphosphine (5 equiv), imidazole (5 equiv), DCM, r.t. 21 h b) 4-hydroxybenzylalcohol (3 equiv), K₂CO₃ (3 equiv), KI (0.03 equiv), DMF, 60 °C, 20 h. c) 4-hydroxybenzaldehyde (2 equiv), triphenylphosphine (2 equiv), DEAD (2 equiv), THF, r.t. 22 h d) Mesyl chloride (20 equiv), pyridine (8 equiv), DCM, r.t., 2 x 1 h. e) 4-hydroxybenzaldehyde (6 equiv), NaOH (5 equiv), DMF, 90 °C, overnight. f) NaBH₄ (5 equiv), *N*-methylmorpholine/ethanol (1:1), r.t. overnight.

3 Synthesis of *N*-aryl piperazines from resin-bound mustards

3.1 *N*-Aryl Piperazine – an important pharmacophore

N- and *N,N'*-substituted aryl piperazines are frequently-encountered pharmacophores in many compounds with different biological profiles.

In the field of the central nervous system (the core area of H. Lundbeck A/S), *N*-aryl piperazines are key compounds for interaction with the 5-HT_{1A} receptor, which plays an important role in the treatment of depression and anxiety.²¹⁶⁻²²¹ Among the drugs containing this structure are the anxiolytic Buspirone and the Wyeth experimental drug Lecozotan (Figure 19).

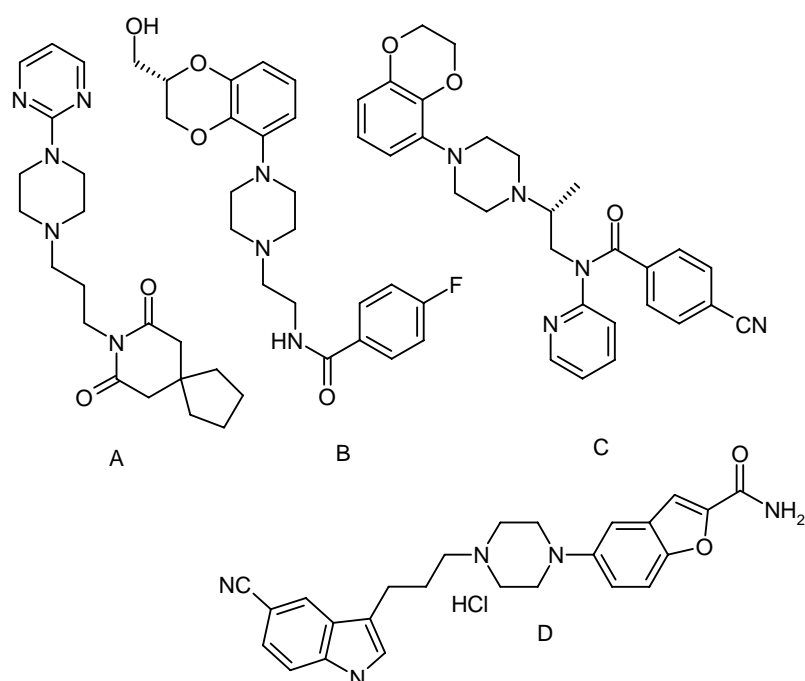


Figure 19: Examples of known anti-depressant and anxiolytic drugs and drug candidates based on the aryl piperazine pharmacophore (A) Buspirone²¹⁸ (B) Flesinoxan²¹⁸ (C) Lecozotan²¹⁹ (D) Vilazodone²²⁰

In addition, *N*-aryl piperazines are very potent agonists of the nicotinic acetylcholine receptors. These receptors are distributed widely throughout the body, and are believed to be involved in the treatment of a number of neurodegenerative diseases, including Alzheimers disease.²²² Compounds containing the *N*-aryl piperazine structure have also been known to bind selectively to the dopamine D3 receptor, an important target in the treatment of Parkinsons disease and the control of substance abuse.²²³⁻²²⁵

Outside the central nervous system the *N*-aryl piperazine pharmacophore is found in several compounds which display α,β adrenoreceptor antagonistic activity.^{226, 227}

Several experimental anti-cancer compounds containing the *N*-aryl piperazine moiety have been identified,^{228, 229} as well as a number of potential anti-osteoporosis drugs.²³⁰

3.2 Synthesis methods for making *N*- Aryl piperazines

Broadly speaking, there are two commonly-used methods for constructing aryl piperazines: the direct addition of piperazine to the ring or the addition of an aniline derivative to a mustard or mustard-like compound. A method based on the intramolecular ring opening of oxazolidin-2-ones has also been reported.²³¹

3.2.1 Reactions with piperazines

The typical synthesis method for *N*-aryl amines today is through Pd- or Ni- catalyzed addition (Buchwald-Hartwig chemistry). Developed in the late nineties by Buchwald and Hartwig separately, these protocols have given high yields under mild reaction conditions and have shown high degree of tolerance to functional groups.²³²⁻²³⁴

Before the Buchwald-Hartwig protocol was developed, aromatic amines were often synthesised by the copper-mediated Ullmann reaction,²³⁵ or through benzyne intermediates²³⁶ but this requires much more forcing conditions, and in the case of benzyne intermediates will often produce more than one regioisomer.

Some activated aryl halides and aryl ethers can add amines directly without catalyst, but this again requires forcing conditions and generally requires activating groups on the resin.^{237, 238}

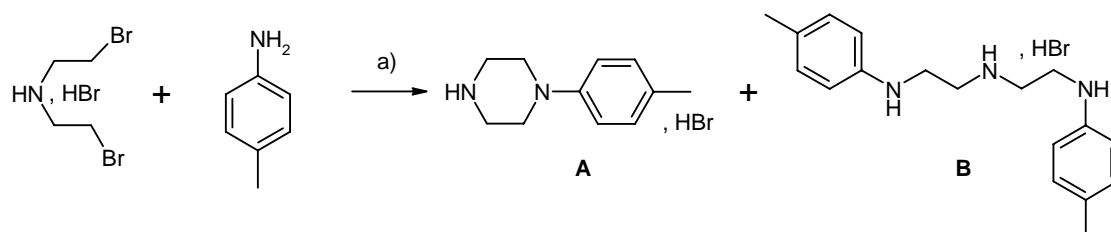
Transition metal complexes with aromatic rings are known to be activated towards nucleophilic addition, and a few *N*-aryl piperazines have been synthesised in this manner,^{239, 240} but these pathways employ a stoichiometric amount of metal and are therefore economically and environmentally unfeasible.

A general problem for the above-mentioned methods of attachment of diamines such as piperazine to aryls is the formation of diarylated product, which lowers the yield and requires separation. This is usually countered with the use of either monoprotected diamines or high excess of reagent.^{241, 242} Some catalytic systems, such as the Ni/bipyridine system developed by Fort *et al.*²⁴³ and the Pd/BINAP system by Gala *et al.*²⁴⁴ have given good yields of monoarylated piperazine with about equimolar amounts of piperazine and reagent.

3.2.2 Piperazine ring formation from mustards

3.2.2.1 *N*-aryl piperazines from mustards in solution

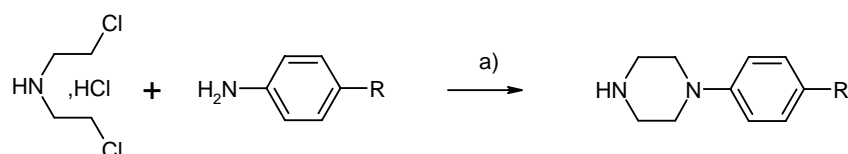
Prelog demonstrated the synthesis of piperazines through base-mediated addition of anilines to mustards in the thirties.^{245, 246} (Scheme 31)



Scheme 31: Prelog's synthesis of 1-(4-tolyl-) piperazine²⁴⁵ a)
bis(bromoethyl)amine, hydrobromide (1 equiv), 4-methylaniline (2 equiv)
methanol, reflux, 12 h. Yield: 85 % **A**, 6 % **B**.

These initial experiments were performed at reflux in methanol or, for the less reactive anilines, in *n*-butanol and gave generally good yields.

Yung *et al.* synthesised a line of aryl piperazines by heating equimolar amounts of mustard and aniline at reflux in ethanol with 2 equivalents of sodium carbonate as a base, to synthesise compounds for antibacterial activity.²⁴⁷ The results are summarized in table 8.

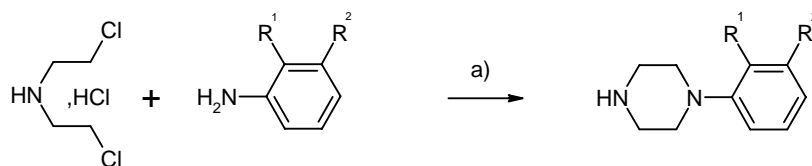


| R- | Reflux time, h | yield, % |
|--------------|----------------|----------|
| Me | 28 | 47 |
| Et | 12 | 32 |
| <i>i</i> -Pr | 51 | 87 |
| <i>t</i> -Bu | 44 | 15 |
| OPh | 45 | 79 |
| F | 46 | 30 |
| Br | 23 | 32 |

Table 8: Aryl piperazine synthesis after Yung *et al.*²⁴⁷ a) bis(chloroethyl)amine, hydrochloride, aniline (1 equiv), Na₂CO₃ (2 equiv), ethanol, reflux, 51 h.

The results show that the reaction is very substrate specific. There is a huge difference in yields between electron-rich and electron-poor anilines, and even between 4-fluoro and 4-bromoaniline, where the reaction is shown to be twice as fast with the less electronegative bromide compared to fluoride.

A later study by Martin *et al* shows that the reaction is dependent on steric and electronic factors.²⁴⁸ (Table 9) There is a marked improvement in yield when the 2-isopropyl group on the aniline is replaced with an isopropyloxy group (table 9, entry 4 and 6), but almost no difference between the yield from the larger *n*-butyl and *n*-butoxy groups in the same position (Table 9, entry 3 and 5) (the latter might in part be a result of the different precipitation agents). Note also the different reactivity of 2- and 3-fluoroaniline (Table 9, entry 7 and 8).



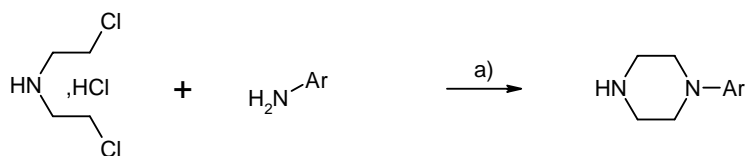
| Entry | -R ¹ | -R ² | Yield (%) | Salt form |
|-------|-----------------|-----------------|-----------|---------------|
| 1 | Et | H | 26 | hydrochloride |
| 2 | nPr | H | 26 | fumarate |
| 3 | nBu | H | 14 | tartate |
| 4 | iPr | H | 21 | fumarate |
| 5 | nBuO | H | 10 | fumarate |
| 6 | iPrO | H | 38 | fumarate |
| 7 | F | H | 27 | fumarate |
| 8 | H | F | 51 | fumarate |
| 9 | H | NO ₂ | 44 | fumarate |

Table 9: Yield from Martin *et al.*s synthesis of aryl piperazines.²⁴⁸ a) bis(chloroethyl)amine, hydrochloride, aniline, n-butanol, reflux, 48 h, then K₂CO₃, reflux, 48 h.

High temperatures are an important factor in these reactions. Brewster *et al.* obtained markedly better yields and purities when they employed 2-butoxyethanol (170 °C) as a solvent instead of n-butanol (116 °C),²⁴⁹ and Orus *et al* obtained a yield of 76% of *N*-(4-nitrophenyl)-piperazine hydrochloride after 24 h at reflux in chlorobenzene (130 °C),²⁵⁰ almost twice the yield obtained by Martin *et al* for the same reaction in n-butanol.²⁴⁸ Orus later used these conditions to synthesise a series of *N*-quinoloylpiperazines, but the yields were generally low.²⁵¹

It is well known that iodine can catalyze the addition of nucleophiles to alkyl chlorides. This method has been used in the addition of anilines to bis(chloroethyl)amine hydrochloride in diglyme (160 °C), but as the procedure was employed as part of a longer reaction sequence yields can not be directly compared to those from other methods. In one case, a yield of 75% of 1-(biphenyl-2-yl)piperazine were obtained in one step after 3.5 h at reflux, which indicates that the use of catalytic iodide can be an improvement of the reaction in general.²⁵²

In a recent study by Liu and Robicaud, it was shown that heating bis(chloroethylamine), hydrochloride and various anilines together without base in diethylene glycol monomethyl ether gave yields > 60% after 6 - 12 hours of heating, even with electron-poor or sterically-hindered anilines.²⁵³ However, no results for electron-poor *and* sterically-hindered anilines, or 2,6-substituted anilines were reported (Table 10).

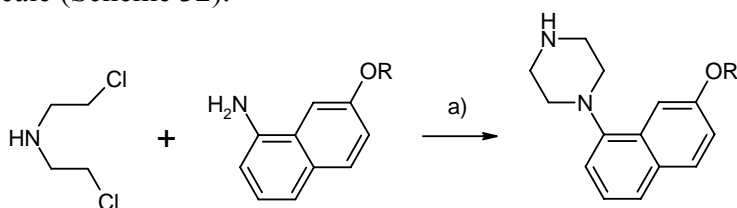


| Ar- | Yield (%) |
|-----------------------------|-----------|
| Phenyl | 79 |
| 4-fluorophenyl | 87 |
| 4-chlorophenyl | 87 |
| 2-methylphenyl | 66 |
| 3-methoxyphenyl | 95 |
| 3-trifluoromethylphenyl | 67 |
| 3,5-ditrifluoromethylphenyl | 65 |
| 4-nitrophenyl | 90 |
| 3-hydroxyphenyl | 87 |
| 3-ethylcarboxyphenyl | 90 |
| 2-naphthyl | 60 |

Table 10: Easy synthesis of aryl piperazines²⁵³ a) ArNH₂ (1 equiv), bis(chloroethyl)amine, hydrochloride (1 equiv), diethylene glycol monomethyl ether, 150 °C, 6-12 h.

Bis(bromoethyl) amine is generally more reactive than bis(chloroethyl) amine, and has been exploited to for instance make radiolabelled compounds.²⁵⁴ However, this increased reactivity can be a problem, as more than one molecule of aniline can be added to the mustard.²⁴⁵ The level of this side product can be suppressed by not adding base to the reaction.^{255, 256} A number of *N*-aryl piperazine syntheses with bis(bromomethyl)amine employing basic alumina as a solid catalyst have given good yields of the *N*-aryl piperazines.^{257, 258}

Very recently Kumar *et al.* performed a very rapid synthesis of an aryl piperazine using microwave heating of the free mustard with poly(ethylene glycol) as the solvent on a 5 mmol scale (Scheme 32).²⁵⁹



Scheme 32: Microwave assisted synthesis of aryl piperazines in poly(ethylene glycol). a) bis(chloroethyl)amine (1 equiv); aminonaphthalen (1 equiv, R = -H or R = -Me), PEG-400, domestic microwave oven (800-1000 W), 3 x 10 s. Yield R = -H 46%, R = -Me: 54%.

3.2.2.2 Neat *N*-aryl piperazine synthesis from mustards

Neat, acidic synthesis of piperazine after the protocol developed by Pollard²⁶⁰ have been employed in the synthesis of many of the simpler *N*-aryl piperazines. Here the aniline, ethanoldiamine and concentrated hydrochloric acid are mixed, and water is distilled off. This avoids the use of toxic mustard, but requires prolonged heating at temperatures above 200°C and gives only modest yields.

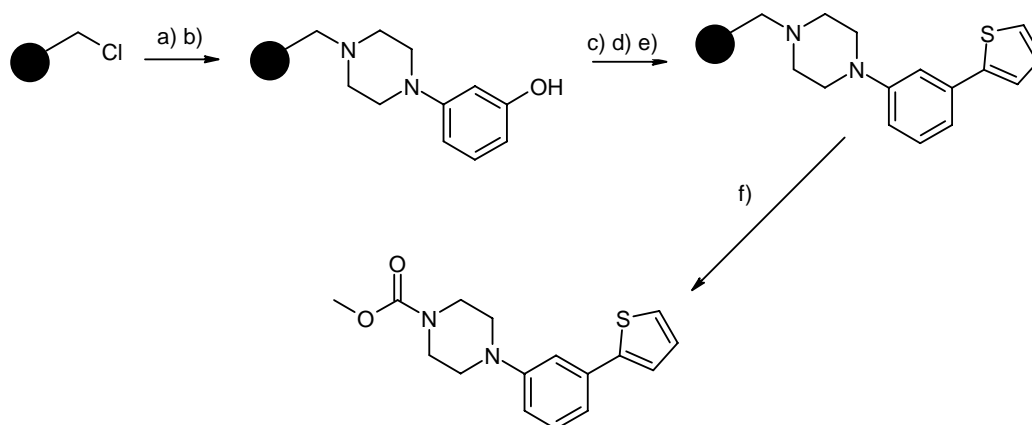
More recently, good yields have been obtained from microwave heating of bis(chloroethyl)amine hydrochloride and anilines (47-73% yields after 1 min of heating at 700 MW).²⁶¹

3.2.3 Solid phase synthesis of aryl piperazines

As amines are key pharmacophores a number of solid phase synthesis routes to amines have been developed,^{19, 262} but relatively few of these make a *N*-aryl piperazine directly on resin.

Unassisted SnAr couplings have been developed both on solid²⁶³ and soluble (PEG) supports,²⁶⁴ and such aromatic C-N coupling reactions have been utilized in the combinatorial synthesis of known drug structures, using Wang Resin.^{265, 266} Forcing conditions are still needed.

Pd-catalyzed Buchwald-Hartwig synthesis have been utilized in the combinatorial synthesis of *N*-aryl piperazines, both with piperazine itself,^{267, 268} and with *N*-aryl piperazine to form *N,N'*-biaryl piperazines²⁶⁹ In a study by Ruhland *et al.* a piperazine was immobilized on resin, and Buchwald-Hartwig chemistry, followed by sequential cross coupling was performed to prepare *N*-biaryl and *N*-teraryl piperazines on resin.²⁷⁰ (Scheme 33)



Scheme 33: Combinatorial synthesis of a diaryl piperazine after Ruhland *et al.*²⁷⁰

a) Merrifield resin, piperazine (10 equiv), *N*-methylmorpholine (5.4 equiv.), THF/DMF (1:1), 60 °C, 16 h; b) 3-bromophenol (15 equiv) Pd₂dba₃ (20 mol %), P(*o*-tol)₃ (30 mol %), potassium *tert*-butoxide (40.0 equiv), toluene, 90 °C, 24 h; c) 4-nitrophenyl triflate (2.5 equiv), K₂CO₃ (2.5 equiv.), 50 °C, 2-3 days; d) bis(pinacolato)diboron (2.5 equiv), PdCl₂(dppf)*CH₂Cl₂ (10 mol %), dppf (5 mol %), dry dioxane, 90 °C, 24 h; e) 2-iodothiophene (6.0 equiv.), Pd(PPh₃)₄ (10 mol %) K₂CO₃ (6.0 equiv), DMF/THF 1/1, 60 °C, 1 d. f) methyl chloroformate, DCM, 0 °C for 30 min, then room temperature for 16 h.

As previously mentioned one of the routes to *N*-aryl piperazines is the nucleophilic addition to metal aryl complexes. Ruhland *et al.* immobilized piperazine on resin and added various iron aryl complexes, thereby avoiding biarylation and making separation of the metal from the reaction easy.²⁷¹

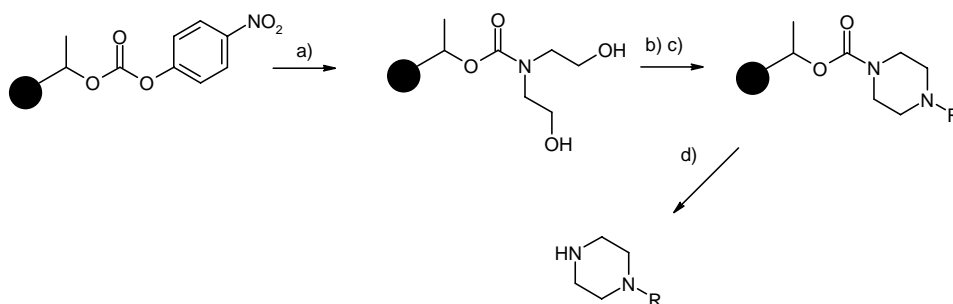
Activation of the phenyl ring has also been achieved by adding phenyl groups to resin-bound bismuth, then cleaving the metal-aryl bond with *N*-aryl piperazine, yielding *N,N'* – diaryl piperazines.²⁷²

Very few examples exist of the direct formation of piperazine rings on resin. A number of 2,5-diketopiperazines have been formed on resin, usually through cyclization- cleavage, where the product is cleaved from the resin by means of nucleophilic ring closure.^{273, 274} An example of large scale solid phase synthesis by such a protocol was described by Raillard *et al.*³¹

An example of piperazine ring formation on resin was demonstrated by Houghten *et al.* who cleaved a 2,3-diketopiperazine from methylbenzhydryl-functionalized resin under reductive condition, thereby obtaining a substituted piperazine ring.^{275, 276}

The on-resin synthesis of unsubstituted piperazine rings through mustard or mustard-like techniques was to the best of our knowledge not known prior to the publication of the work presented in this thesis.²⁷⁷ An article by Dolle *et al* that describes the synthesis of piperazines from resin-bound bis-mesylated diethanolamine was

published in 2006, but no aryl piperazines were formed using this method²⁷⁸ (Scheme 34).



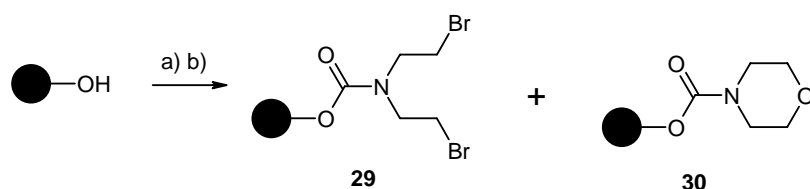
Scheme 34: Solid-phase piperazine synthesis on α -methylbenzyl polystyrene resin after Dolle *et al.*²⁷⁸ a) diethanolamine (5 equiv), diisopropyl ethylamine (20 equiv), 60 °C, 44 h; b) mesyl chloride (11 equiv), diisopropyl ethylamine (13 equiv), *N,N*-dimethylaminopyridine (0.6 equiv), DCM, 0 ° C \rightarrow r.t., overnight c) RNH₂ (10 equiv), DIPEA (20 equiv), NMP, microwave, 160°C, 30 min. d) trifluoroacetic acid/DCM 1:1, 1h.

3.3 Experimental work

3.3.1 Immobilization of mustards

Both bis(chloroethyl)amine, hydrochloride and bis(bromoethyl)amine, hydrobromide were available as starting materials for the piperazine formation on resin. Bis(chloroethyl)amine, hydrochloride is commercially available and bis(bromoethyl)amine, hydrobromide is custom-made for H. Lundbeck A/S for synthesis purposes. The latter mustard is more reactive than the first, but it is delivered in a form mixed with morpholine, which needs to be removed through recrystallization. As this is a rather cumbersome process it was quickly decided to use the commercially-available product.

The mustard was initially immobilized by adding a 5-fold excess of bis(bromoethyl)amine hydrobromide and a 15-fold excess of triethyl amine in dichloromethane to form **29**.²⁷⁹ Immobilization proceeded to completion overnight as determined by ¹³C gel-phase NMR (Table 11, entry 1). Later Br-elemental analysis of the resin showed only 80% loading of the mustard. ¹³C gel-phase NMR and elemental analysis (nitrogen content higher than bromide content/2) indicated either that the remainder of the chloroformyl groups had reacted with the morpholine which was still present in the starting material or that **29** have hydrolyzed and formed resin-bound morpholine **30** under the reaction conditions. This was later confirmed by reacting morpholine with **4** for spectral comparison.



| Entry | equiv. phosgene | equiv. mustard | base | other conditions | NMR yield ^a | Yield ^b |
|-------|--------------------|-------------------|---------------------------------------------|--------------------------------|---------------------------|--------------------|
| 1 | 12 | 5 | triethylamine (15 equiv) | dry DCM, r.t., 24 h | 100% ^c | 90% |
| 2 | 5 | 5 | triethylamine (5 equiv) | water, r.t., overnight | ca. 100% | 114% |
| 3 | 5 | 2 | triethylamine (6 equiv) | water, r.t., 19 h | 56% | 58% |
| 4 | 2 | 2 | K ₂ CO ₃ (3 equiv) | water, 80 ° C, overnight | 0 % | N/A |

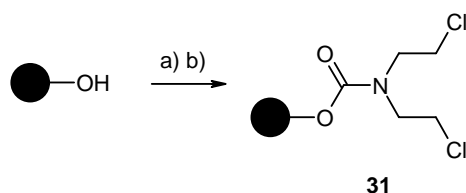
Table 11: Immobilization of mustard on resin. a) Phosgene (20 % w/w in toluene), r.t. b) bis(bromoethyl)amine, hydrobromide, base. ^a Extent of reaction with resin estimated from ¹³C gel-phase NMR ^b Yield of **29** estimated from Br - elemental analysis ^cSpectrum also contains resin-bound morpholine **30**.

As chloroformates are known to be quite stable in water it was decided to replace dichloromethane with water under the same conditions. This turned out to be an improvement, as the yield by Br-analysis increased to 112% (Table 11, entry 2). The most likely reason for this improvement is the reagent concentration effect, which presumably concentrated both the hydrophobic mustard and amine base inside the resin. The >100% yields with respect to the loading determined by the Fmoc-glycine method, can be explained by the fact that the large Fmoc-glycine molecule cannot access some of the more hindered hydroxyl groups in the resin, and so therefore the effective loading of hydroxyl groups will be larger than specified by the manufacturer in reactions with small molecules such as phosgene and mustard.

The initial route employing 5 equivalents of mustard and 15 equivalents of triethyl amine could easily be applied to high-loading resin on a 0.15 mol scale. However, for scale-up purposes a route employing fewer equivalents of reagents was desirable. An initial screening experiment with a lower amount of mustard (2 equivalents) did not proceed to completion at room temperature (Table 11, entry 3). Heating the reaction to reflux²⁸⁰ did not give any reaction by ¹³C gel-phase NMR, but resulted in regeneration of the starting resin (Table 11, entry 4). It was later discovered that the resin-bound mustard is not stable in warm aqueous base, but as no product was

detected on resin during the early stages of the reaction, the unsatisfactory reaction was more likely the result of hydrolysis of the chloroformyl linker.

A screening experiment with various bases (Table 12) showed that complete immobilization could be reached with 2 equivalents bis(chloroethyl)amine hydrochloride and 6 equivalents of potassium carbonate, and this route was chosen for future scale-up purposes, although 3.5 equivalents of bis(chloroethyl)amine, hydrochloride was employed in most experiments, due to an initial miscalculation.



| Entry | base | Amount | NMR Peak height (64 ppm) | NMR Peak height (61 ppm) | NMR conversion |
|-------|--------------------------------|----------------|--------------------------|--------------------------|----------------|
| 1 | triethylamine | 3.2 mL (2.4 g) | 59 mm | - | full |
| 2 | K ₂ CO ₃ | 3.2 g | 55 mm | - | full |
| 3 | pyridine | 1.9 mL (1.8 g) | - | 35 mm | none |
| 4 | DIPEA | 2.4 mL (3.0 g) | 75 mm | - | full |

Table 12: Screening of various bases in the immobilization of mustard. a) phosgene (20 % w/w in toluene, 2.5 equiv), THF, 2.5 h. b) bis(chloroethyl)amine, hydrochloride (2 equiv), base (6 equiv), water, r.t., 4 h.

It should be noted that the resin-bound mustards are quite stable. After 8 month of storage in a closed container no difference was seen in the ¹³C gel-phase NMR spectrum of the resin-bound chloromustard **31**. The ¹³C gel-phase NMR spectrum of **29** showed a small amount of hydrolysis after 6 month.

3.3.2 Synthesis of various *N*-Aryl piperazines

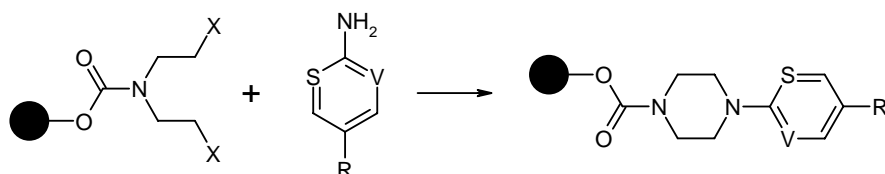
3.3.2.1 Initial experiments

4-Fluoroaniline was chosen for the initial experiments, as it is easy to detect on resin with ^{19}F NMR spectroscopy. It is a liquid at room temperature and therefore convenient for the investigation of the reagent concentration effect in water (Table 13, entry 1 and 2). The reaction was initially performed at room temperature, as it was believed that the reagent concentration effect would help force the reaction to completion. NMR and later elemental analysis showed that the desired resin-bound piperazine **32** was formed, but a significant amount of mustard **29** was still present. The yield was determined as 47% by fluorine elemental analysis. Later scaling up to gram-scale of this reaction, followed by reductive cleavage and purification by precipitation with oxalic acid yielded only 9 % of the corresponding 1-(4-fluorophenyl)-4-methylpiperazine **33** (and *ca.* 20 % of the final product was found to be by products from addition of two aniline molecules to the mustard: bis(*N*-(4-fluoroanilinoethylene)amine (**34**) and *N*-methyl bis(*N*-(4-fluoroanilinoethylene)amine (**35**)).²⁸¹

Reaction with the more-nucleophilic 4-iodoaniline (a good precursor for further reactions) to form **36** did not run to completion (Table 13, entry 3). Heating the reaction at reflux gave complete conversion, but yielded only a small amount of 1-(4-iodophenyl)-4-methylpiperazine (**37**) upon reductive cleavage (table 13, entry 4). Judged by ^{13}C gel-phase NMR a significant amount of cleavage had occurred during the piperazine-formation step. Synthesis with electron-rich methoxyaniline to form **38** also resulted mainly in cleavage (table 13, entry 8).

Attempted synthesis with amino- substituted heteroaromatics 2-aminopyridine and 2-aminopyrimidine gave no detectable yield of resin-bound piperazines **39** and **40** (Table 13, entry 9-10). Upon heating of the reaction only hydrolysis of mustard **29** to **30** was seen (Table 13, Entry 11)

Experiments with resin-bound bis(chloroethyl)amine **31** gave the same picture (Table 13: entry 6 and 7): very low yields, even when catalytic iodide was added, and significant cleavage. It was decided to investigate the addition in more detail. Experiments showed that the resin-bound product was stable under the reaction conditions, and an experiment where resin-bound mustard was treated under reaction conditions (but in the absence of an aniline) showed reasonable stability (no significant changes in the ^{13}C gel-phase NMR spectrum after 4 hrs).



| Entry | -X | S | V | -R | Conditions | Result | Prod |
|-------|----|----|----|-----|-------------------------------------------------------------------------------------------------------------|----------------------------|------------------------|
| 1 | Br | CH | CH | F | 4-fluoroaniline (8 equiv), K ₂ CO ₃ (3 equiv), water, r.t., overnight. | 47% ^a | 32 |
| 2 | Br | CH | CH | F | 4-fluoroaniline (6 equiv), K ₂ CO ₃ (3 equiv), water, r.t., 21 h. ^b | 30% conv. ^c | 32 ^d |
| 3 | Br | CH | CH | I | 4-iodoaniline (5 equiv), K ₂ CO ₃ (2.5 equiv), water/MeCN (3:1), r.t., 24 h. | 21% conv. ^c | 36 ^e |
| 4 | Br | CH | CH | I | 4-iodoaniline (6 equiv), K ₂ CO ₃ (2.5 equiv), water /MeCN (3:1), 78 °C, 21 h. | 100% cleavage ^c | 36 |
| 5 | Br | CH | CH | F | 4-fluoroaniline (5 equiv), K ₂ CO ₃ (2.5 equiv), water, 100 °C, 18 h. | 89 % cleavage ^c | 32 |
| 6 | Cl | CH | CH | F | 4-fluoroaniline (5 equiv), K ₂ CO ₃ (3 equiv), water, 100 °C, 17 h. | 91 % cleavage ^c | 32 |
| 7 | Cl | CH | CH | F | 4-fluoroaniline (5 equiv), K ₂ CO ₃ (3 equiv), KI (0.2 equiv), water, 100 °C, 23 h. | 87 % cleavage ^c | 32 |
| 8 | Br | CH | CH | OMe | 4-methoxyaniline (5 equiv), K ₂ CO ₃ (2.5 equiv), water, 60 °C, 18 h. | 55% cleavage ^c | 38 |
| 9 | Br | N | CH | H | 2-aminopyridine (5 equiv), K ₂ CO ₃ (2.5 equiv), water, r.t., 26 h. | no reaction | 39 |
| 10 | Br | N | N | H | Pyrimidin-2-ylamine (5 equiv), K ₂ CO ₃ (2.5 equiv), water, r.t., overnight | no reaction | 40 |
| 11 | Br | N | N | H | Pyrimidin-2-ylamine (5 equiv), K ₂ CO ₃ (2.5 equiv), water, microwave, 100 °C, 6 min. | 30 formed | 40 |

Table 13: Initial piperazine synthesis experiments. ^aYield by F elemental analysis. ^b Gram-scale ^c Conversion by comparison of relative height of mustard and piperazine peaks in ¹³C gel-phase NMR spectrum. ^d Reductive cleavage yielded ca. 9 % of a mixture of **33** and **34/35** (20 % by UV₂₅₄).

^d Cleavage extent estimated by comparison of the relative heights of -CH₂OH and -CH₂OR peaks in the ¹³C gel-phase NMR spectrum ^e Crude yield of corresponding 1-(4-iodophenyl)-4-methylpiperazine **37** after reductive cleavage < 6 %

It is known that the reaction between amine and mustard can form an oxazilodin-2-one by-product from the monoalkylation of the mustard.²⁸² Upon investigation of the washing from the resin a significant amount of a carbonyl-containing by-product was found, but after purification it was discovered that the main impurity was not the expected oxazilodin-2-one **41** but instead the previously unknown imidazol-2-one **42** (Figure 17) formed by addition of two aniline molecules to the mustard and cyclative cleavage.

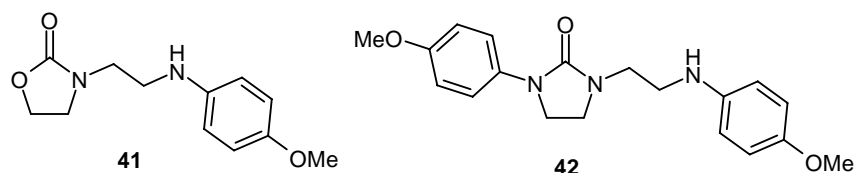
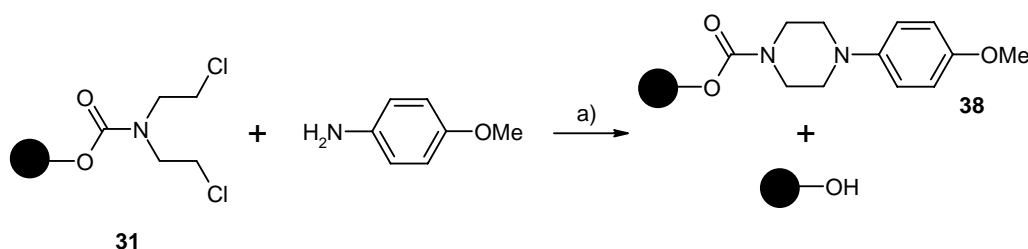


Figure 17: The expected oxazilodin-2-one byproduct (**41**) and the actual main by product, the imidazol-2-one (**42**).

The mechanism and possible use of this interesting and previously-unknown side reaction will be described in detail in a later chapter.

It is believed that this side reaction is the result of the reaction concentration effect being too efficient in water and favouring the second addition of aniline.

Various other, less-polar solvents were tried and the resin products were analyzed using the short NMR method (1024 scans) (Table 14).



| Entry | Solvent | 61 ppm peak height | 64 ppm peak height | Cleavage (calculated) |
|-------|-------------------|--------------------|--------------------|-----------------------|
| 1 | DMF | 12 mm | 12 mm | ~50% |
| 2 | THF | - | - | - |
| 3 | MIBK | 3 mm | 23 mm | ~10% |
| 4 | Water | 9 mm | 3 mm | ~75% |
| 5 | <i>n</i> -butanol | 12 mm | 2 mm | ~90% |
| 6 | Ethanol | 42 mm | 12 mm | ~80 % |
| 7 | DME | 4 mm | 27 mm | ~10 % |

Table 14: Solvent screening for minimizing cleavage from resin in the synthesis of **38** a) 4-methoxyaniline (5 equiv), K₂CO₃ (2.5 equiv), KI (0.2 equiv), 80 °C, overnight.

It appeared that the best solvents for the piperazine formation were polar, non-nucleophilic solvents. Methyl isobutyl ketone (MIBK) was chosen as it has a higher boiling point than DME, which is the only other solvent of those examined that

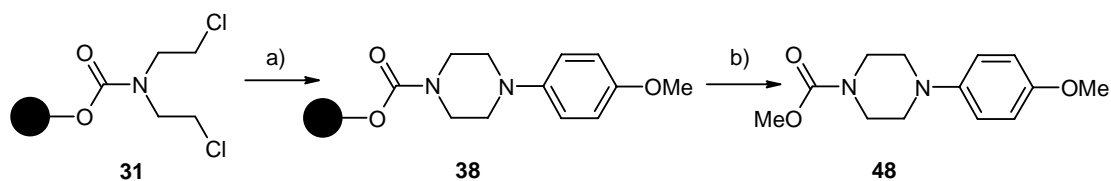
suppressed cleavage to less than 50%. MIBK has been used previously as a solvent in these kinds of reactions.^{283, 284} As no data existed on the swelling of Versabeads in MIBK, the swelling of resin **31** in MIBK was measured by the syringe method and found to be acceptable (2.3 mL/g).

Initial experiments in MIBK on a larger scale showed incomplete reaction even after reflux overnight (117°C). It appeared that the potassium carbonate was not sufficiently soluble in MIBK, so after screening various liquid bases pyridine was chosen as a replacement. To lower the risk of solvent boiling away during the long reaction times and to keep the concentration of pyridine (b.p. 115 °C) in solution high a reaction temperature slightly lower than reflux (100 °C) was chosen.

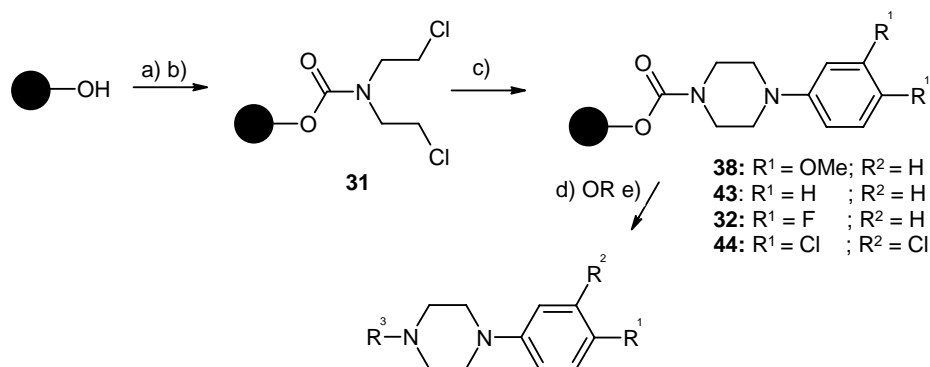
With these conditions and the cleavage conditions previously described, a series of *N*-aryl and *N*-aryl-*N'*-methyl piperazines were synthesized (Table 15). The reactions were monitored conveniently by ¹³C gel-phase NMR. As expected, the required reaction times for complete reaction of the mustard were very dependent on the nature of the aniline used, with the longest reaction times necessary for the electron-deficient 3,4-dichloroaniline, which needed 112 h to give a complete reaction.

The reaction yields were fair to good, especially for **46a**, which after basic cleavage could be isolated as a CHN-pure product in 60% overall yield (88 % average yield pr. step) after aqueous workup (Table 15, entry 1)). Some of the yields of secondary amines were lowered due to the accidental presence of methanol during the cleavage reaction, yielding a significant amount of the corresponding *N*-methyl carbamate, which was separated through precipitation of the desired piperazine with oxalic acid.

To demonstrate that cleavage to give carbamates is a useful reaction, the *N*-methyl carbamate of 1-(4-methoxyphenyl)-piperazine **48** was obtained by cleavage in methanolic potassium hydroxide yielding 32% of CHN-pure compound upon aqueous workup (Scheme 35).



Scheme 35: Synthesis of a methyl carbamate through nucleophilic cleavage. a) 4-methoxyaniline (5 equiv), pyridine (5 equiv), KI (5 equiv), MIBK, 100°C, 15 h, b) KOH (10 equiv), methanol, reflux, 3.5 h. Yield: 32%

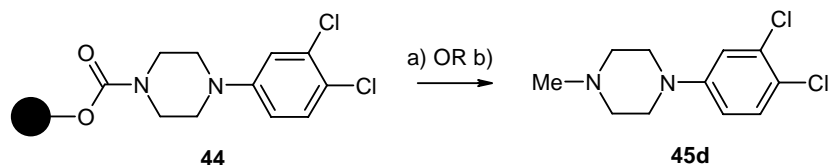


| Entry | Compound | -R ¹ | -R ² | -R ³ | Reaction time, step c) (h) | Crude yield ^a (%) | Crude purity ^b (%) | Purified yield (%) |
|-------|-------------------------|-----------------|-----------------|-----------------|-------------------------------|---------------------------------|----------------------------------|-----------------------|
| 1 | 45a | OMe | H | Me | 28 | 60 ^c | 100 | 60 ^c |
| 2 | 45b | H | H | Me | 86 | 50 | 75-80 ^d | 37 |
| 3 | 45c ^e | F | H | Me | 49 | 41 | 99 | 21 |
| 4 | 45d | Cl | Cl | Me | 112 | 22 | ca. 60 ^{d,f} | 4 |
| 5 | 46a | OMe | H | H | 32 | 46 | 55 ^g | 20 ^h |
| 6 | 46b | H | H | H | 60 | 40 | ca 70 ^{dg} | 17 ^h |
| 7 | 46c | F | H | H | 66 | 39 | 77 | 23 ^h |
| 8 | 46d | Cl | Cl | H | 111 | 34 | 85 | 6 ^h |

Table 15: Yield of aryl piperazines synthesised on resin on gram-scale. a) phosgene (20 % w/w in toluene, 2 equiv), THF, r.t., 2h; b) bis(chloroethyl)-amine, hydrochloride (3.5 equiv), K₂CO₃ (6 equiv), water, r.t., 6 h; c) aniline derivative (5 equiv), pyridine (10 equiv), KI (0.2 equiv), MIBK, 100 °C; d) (Entry 1-4) LiAlH₄ (10 equiv), THF, reflux, overnight; e) (entry 5-8) potassium *tert*-butoxide (2 equiv), DME, reflux, 3 h.

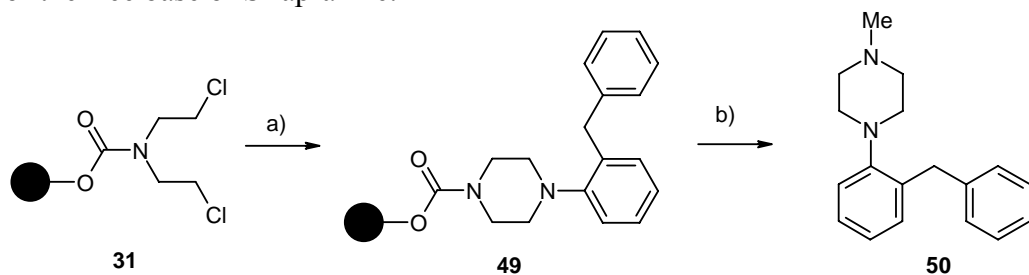
^aOverall yield based on 1.97 mmol/g loading of Versabeads™ ^bPurity from HPLC ^cCHN pure ^dDue to problems from overlapping peaks on the HPLC, the crude purity is estimated from ¹H NMR ^e same structure as **33** ^f10-15 % of 1-(4-chlorophenyl)-4-methylpiperazine **47** was also present. ^gDue to contamination of the DME with methanol a significant amount of the corresponding methyl carbamate was formed (Entry 5: 35 %, entry 6: 5-10 %) ^hIsolated as the corresponding oxalate.

A problem was encountered in the reductive cleavage of resin **44**. A significant amount of 1-(4-chlorophenyl)-4-methylpiperazine **47** (10-15 %) was found in the final product, and had to be separated through Kugelrohr distillation. The cleavage of chlorine from aromatic rings under reductive conditions is a well-known phenomenon.²⁸⁵ A later microwave screening reaction using the milder, more oxophilic reagent $\text{Zn}(\text{BH}_4)_2$, generated *in situ*²⁸⁶⁻²⁸⁸ did not form any of the monochlorophenyl by-product, but complete cleavage from the resin was not achieved under these conditions. The crude product appeared to be a mixture of the expected product **45d** and some kind of complex of this, possibly the boronic acid salt (Scheme 36).



Scheme 36: Cleavage of carbamate linker with zinc borohydride. a) NaBH_4 (3 equiv), ZnCl_2 (1.5 equiv), THF, microwave, 110 °C, 30 min b) NaBH_4 (6 equiv), ZnCl_2 (3 equiv), THF, reflux, 3 h.

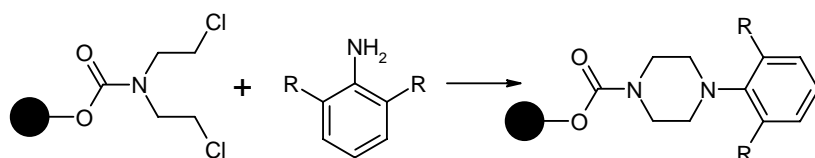
To prove that the method could be employed in the synthesis of a known drug, the free base of the Ferrer experimental antidepressant Sifaprazine²⁸⁹ was synthesised (Scheme 37). The 2-benzylaniline used for this synthesis is very sterically hindered, and an initial experiment using the standard conditions (Table 15) gave a crude yield of approximately 10%. The reaction was optimized using microwave heating and it was found that adding iodide in excess instead of as a catalytic amount (3 equivalents) accelerated the reaction. The reaction was repeated using these conditions yielding 2.7 % of the free base of Sifaprazine.



Scheme 37: Synthesis of Sifaprazine free base **50** on solid phase a) 2-benzylamine (5 equiv), pyridine (10 equiv), KI (3 equiv), MIBK, 100°C, 76 h. b) LiAlH_4 (10 equiv), 1 M in THF, reflux, 19 h, 2.7 %

Reaction with the even more sterically-hindered 2,6-dimethylaniline to give resin-bound compound **51** was tried, but did not run to completion. After 6 days of reaction only 25% conversion was seen in the ^{13}C gel-phase NMR spectrum (Table 16, entry 1). An experiment with microwave heating after 6 hrs at 150 °C gave full conversion, but an unclear ^{13}C gel-phase spectrum, and a later cleavage experiment yielded a very small amount (< 2 %) of a complicated mixture of products (Table 16, entry 2).

An experiment with microwave-assisted ring closure of the more-nucleophilic 2,6-dimethoxyaniline yielded only very small conversion, confirming the predominance of steric factors over electronic in this type of reaction (Table 16, entry 3).



| Entry | R | Conditions | Conversion | Compound |
|-------|-----|----------------------------------------------------------------------------------------------------|-----------------------|-----------|
| 1 | Me | 2,6-dimethylaniline (5 equiv), pyridine (10 equiv), KI (0.2 equiv), MIBK, 90 °C, 6 days. | 25 % | 51 |
| 2 | Me | 2,6-dimethylaniline (5 equiv), pyridine (10 equiv), KI (0.2 equiv), MIBK, microwave, 150 °C, 6 h. | complete ^a | 51 |
| 3 | MeO | 2,6-dimethoxyaniline (5 equiv), pyridine (10 equiv), KI (0.2 equiv), MIBK, microwave, 150 °C, 1 h. | 12 % | 52 |

Table 16: Attempted piperazine formation with 2,6-disubstituted aniline derivatives

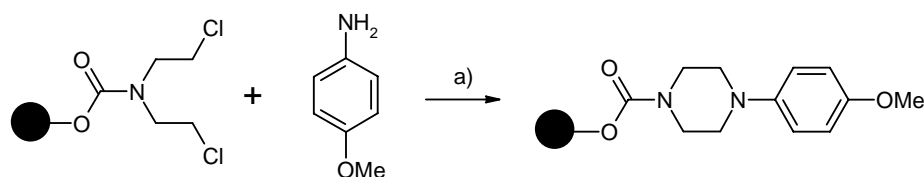
^aConversion was complete, judged by ¹³C gel-phase NMR, but the yield upon cleavage (potassium *tert*-butoxide, DME, microwave) was very low, and gave a mixture of products.

3.3.3 Scale-up of the piperazine reaction

3.3.3.1 Condition optimization using microwave chemistry

The high-yielding synthesis of **45a** was chosen to demonstrate scale-up on resin. The route needed some modifications before it could be scaled up. Using a 5-fold excess of 4-methoxyaniline was clearly not desirable on a larger scale, as was the addition of a large amount of solid lithium aluminium hydride before heating to reflux. When working on a larger scale it is generally preferable to add reagents as solutions, in order to maintain good control over the addition and avoid problems with dust. It is also preferable to add reagents to the reaction mixture after heating it to the desired reaction temperature to minimize the risk of runaway reactions.²⁹⁰ The use of a large amount of phosgene solution was clearly undesirable as well, and at least had to be supplied in a safer form.

As previously mentioned, the reaction between **31** and 2-benzylaniline was favoured by the use of an excess of potassium iodide. A short series of microwave reactions was set up and evaluated using ¹³C gel-phase NMR to find optimum conditions (Table 17).



| Entry | equiv. 4-MeO- aniline | equiv. pyridine | equiv. KI | Peak height 41 ppm (mm) | Peak height 43 ppm (mm) | Conversion |
|-------|-----------------------------|--------------------|--------------|----------------------------------|----------------------------------|------------|
| 1 | 2 | 4 | 4 | | | complete |
| 2 | 1.2 | 2 | 0.4 | - | - | low |
| 3 | 1.5 | 3 | 1 | 73 | 15 | ~20% |
| 4 | 2 | 4 | 2 | 25 | 30 | ~55% |
| 5 | 2 | 4 | 1 | 73 | 20 | ~20% |

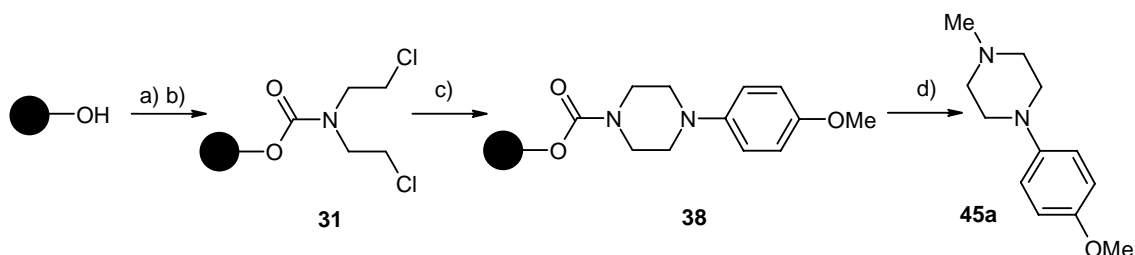
Table 17: Microwave-assisted screening of conditions for optimizing the synthesis of 1-methyl-4-(1-methoxyphenyl)-piperazine. a) MIBK, microwave, 150 °C, 1 h.

In a cleavage-optimization experiment, resin from Table 17, entry 1 was cleaved by suspending the resin in a commercially-available 1 M solution of lithium aluminium hydride in THF and heating with microwaves. Complete cleavage was achieved using only 4.2 equivalents of lithium aluminium hydride under conditions corresponding to 4 h at reflux. Likewise, water was replaced with the less-reactive ethyl acetate as a quenching agent. The final crude yield of 32% was acceptable.

The use of triphosgene, decomposed to phosgene by heating to 50 °C in THF,^{180, 181} was found to be the most acceptable alternative to the commercial solution of phosgene in toluene. In addition complete substitution of the resin could be achieved with only 1.5 equivalents of triphosgene and 1.5 equivalents of mustard, as judged by ¹³C gel-phase NMR.

Upon scaling these conditions to gram-scale a yield of 39 % of the 1-methyl-4-(4-methoxyphenyl) piperazine was obtained. This yield was lower than expected (previous experiments had given 60 %) and this was attributed to the formation of chloroformyl handle **4** being slower with triphosgene than with phosgene.

Using the same optimized conditions, but with 3 h reaction time to form the chloroformyl linker the reaction was performed on a 0.19-mol scale (100 g Versabeads) and yielded the test compound in an overall yield of 21.1 g (55%) (Scheme 38).



Scheme 38: The large-scale (100 g Versabeads (0.19 mol)) solid-phase synthesis of 1-methyl-4-(1-methoxyphenyl)-piperazine **45a** a) triphosgene (0.5 equiv), THF, 50 °C, 3 h. b) bis(chloroethyl)amine, hydrochloride (1.5 equiv), K₂CO₃ (4 equiv), r.t. 4 h. c) 4-methoxyaniline (2 equiv), pyridine (5 equiv), KI (4 equiv), MIBK, 100 °C, 28 h. d) LiAlH₄ (4.2 equiv), THF, reflux, 4 h. Overall yield: 55%

3.3.4 Discussion of resin stability and resin re-use

For solid-phase synthesis to be a useful tool in initial development chemistry, the resin must be reusable, otherwise the high initial cost of the resin would render the process un-economic.

Resins based on the SPOCC structure are known to be highly chemically stable. Initial experiments by Meldal *et al* showed that their SPOCC resin beads were stable to concentrated hydrochloric acid, *n*-butyllithium and heating at reflux with thionyl chloride in toluene.²⁹¹

The resin had also demonstrated a high degree of mechanical stability, being quite stable against the gentle magnetic stirring used in smaller-scale preparations. More vigorous magnetic stirring resulted in visible breakdown of the beads.

After reductive cleavage the beads had gained a brownish colour, whereas they turned completely black after cleavage with base. Examination of the beads by ¹³C gel-phase NMR showed no differences to the starting beads. The excess aluminium salts present in the resins from reductive cleavage could easily be removed by suspending the resin in 4 M hydrochloric acid overnight.

To demonstrate the stability of the resin, some of the resin from the gram scale experiment was reused after cleavage in the same reaction under the same conditions, but on a smaller scale. The resin loss can be attributed to removal of resin for NMR monitoring and elemental analysis and some was lost clinging to glassware. Loss due to beads being grinded down to a smaller size than the filter cannot be ruled out, as traces of dark material had been observed in several reactions. The yield was almost the same as in the first cycle (38 %), but the resin gained an even darker colour and elemental analysis revealed significant increase in its nitrogen content. The latter was probably from aniline polymers trapped in the resin matrix. This did not seem to affect the yield, but might potentially effect a gradual change in the physical properties of the resin. Such changed properties could account for the fact that more broken beads were found in the reused resin (Figure 18), but this could also simply mean that damaged beads had accumulated over two cycles instead of one, or that the magnetic stirring employed in the second cycle had been too vigorous.

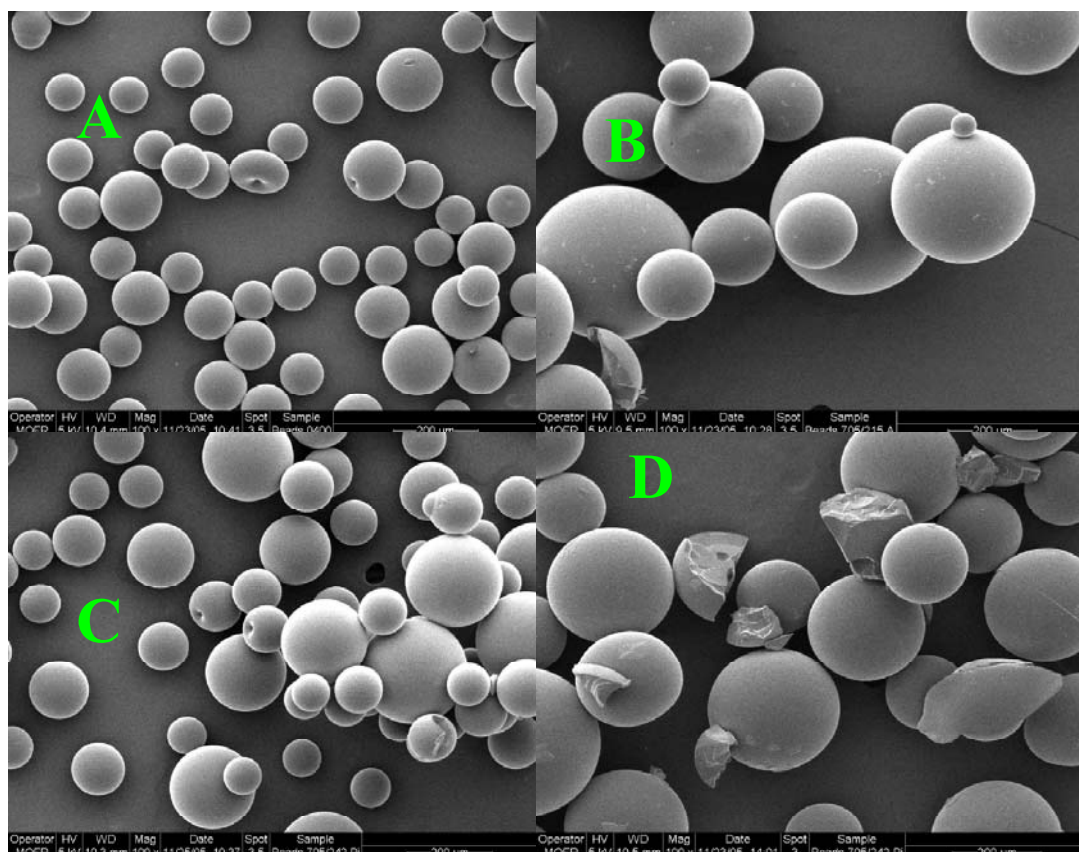


Figure 18: Electron microscope images of resin before reaction (A), after mustard immobilization (B), after one reaction cycle (C) and after two reaction cycles (D). Enlarged 100 times.

4 Synthesis of an imidazolidin-2-one by cyclative cleavage

Cyclative cleavage is a well-established technique to form heterocycles on solid-phase.^{19, 273} It is especially desirable because the resulting compounds do not need to contain any memory of the linkage to the resin (so-called traceless synthesis). The large amounts of the previously unknown imidazolidin-2-one **42**, which was produced as by-products when performed in water prompted an investigation into the mechanism of the reaction.

4.1 *Synthesis and application of imidazolidin-2-ones*

N-phenyl substituted imidazolidin-2-ones are interesting compounds, as they are a structural feature of many biologically active compounds, for example antiparasitics²⁹², antivirals²⁹³ and CNS active compounds.^{294, 295} The antischizophrenic Zetidoline is an example of a commercially available drug, containing the structure (Figure 19).²⁹⁶

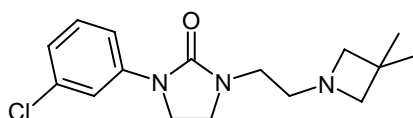
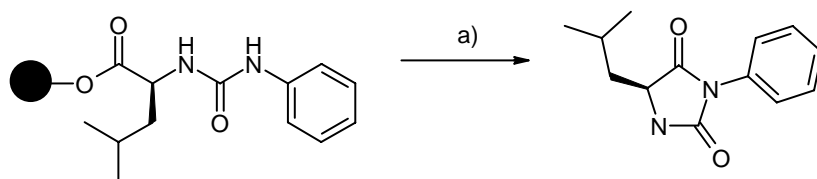


Figure 19: Zetidoline²⁹⁶

In solution phase chemistry imidazolidin-2-ones can be prepared by the same methods as other ureas. The most common routes are *via* the condensation of ureas with diamines.²⁹⁷ A number of other routes to these compounds have been developed^{297, 298}, including the reaction of phosgene or phosgene equivalents with diamines,^{295, 299} addition of isocyanates,^{297, 298, 300} selective reduction of imidazilodin-2,4-diones,³⁰¹ oxidative carbonylation,²⁹⁸ addition of lithiated *n*-BOC amines to imines or from tert-butyl nosyloxycarbamate.^{302 303}

A number of solid-phase syntheses of imidazilodin-2,4-diones are known, many employing cyclative cleavage.^{19, 274} It has been reported that protic solvents promote the cyclative cleavage of hydrantoin from resin, but only for *N*-aryl ureas³⁰⁴ (Scheme 39).



Scheme 39: Cleavage of hydrantoin from TentaGel resin. a) water, 65°C, 4 h, 87 % yield.³⁰⁴

The solid-phase synthesis of imidazolidin-2-one structures on solid phase are less extensively reported and generally use phosgene equivalents to generate the imidazolidin-2-one moiety.^{276, 305-308} A solid-phase synthesis based on isocyanate has also been published.³⁰⁹

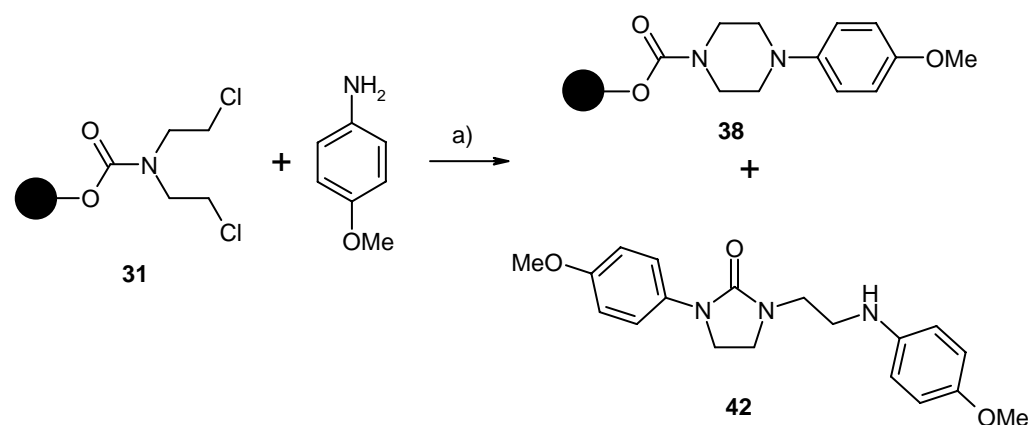
4.2 Mechanistic investigation

Elucidating the mechanism behind the reaction between aniline and mustard reagent in polar solvents is not simple, given that a number of possible reaction routes exist, and it is not immediately obvious which one will be predominant (Figure 20).

Two main parameters were monitored in the experimental work directed towards the elucidation of the mechanism. They were (a) the yield of cyclic urea, which was isolated from the reaction mixture by automated flash chromatography, and (b) the extent of cleavage from the resin, as estimated from the height of the relevant peaks in the ¹³C gel-phase NMR spectrum.

4.2.1 Preliminary experiments

Preliminary experiments with various amounts of iodide seem to indicate a slight increase in the yield upon increase of the amount of iodide (Table 18).



| entry | equiv KI | 64 ppm peak height (mm) | 61 ppm peak height (mm) | Cleavage (%) | Yield 37 (%) |
|-------|----------|-------------------------------|-------------------------------|-----------------|---------------------------|
| 1 | 0.2 | 23 | 43 | 65 | 36 |
| 2 | 1.0 | 14 | 35 | 71 | 42 |

Table 18: a) 4-methoxyaniline (5 equiv), K₂CO₃ (2.5 equiv), KI, water, 80°C, 23 h.

^a Estimated from ¹³C gel-phase NMR spectrum.

A number of by-products were formed in trace amounts and identified by NMR (figure 21):

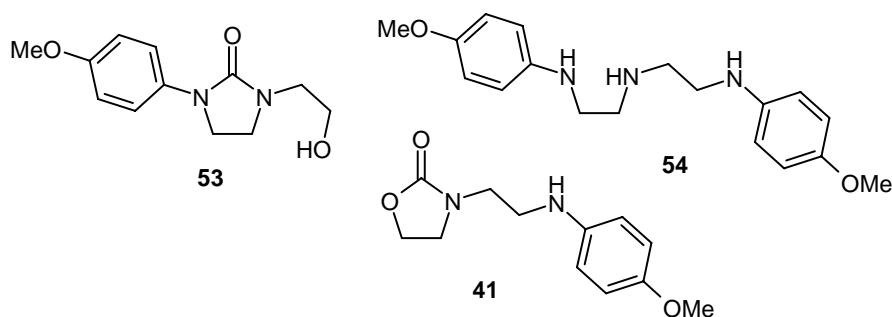
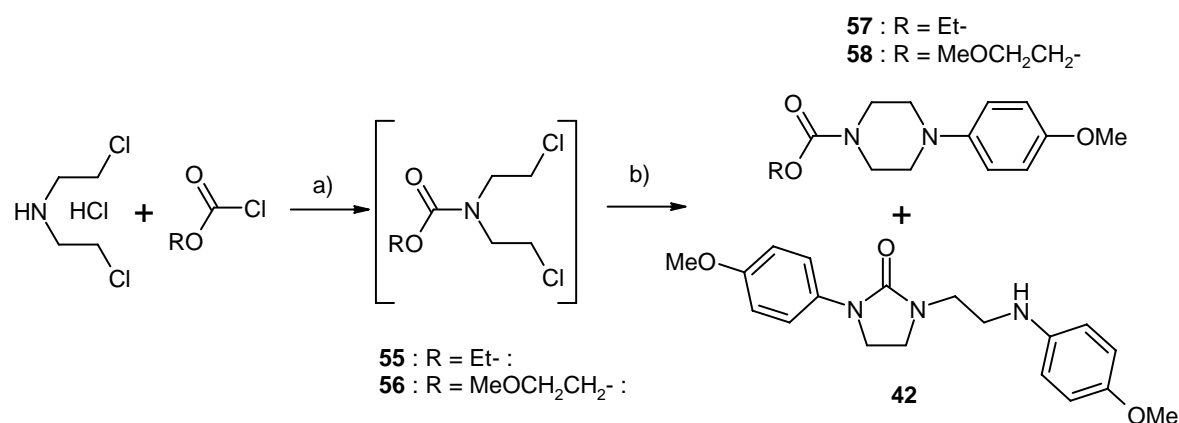


Figure 21: Hydrolysis byproducts (**41** and **53**) and product from incomplete imidazolidin-2-one formation (**54**) found in table 18, entry 2.

4.2.2 Cyclative cleavage in solution-phase vs. solid-phase

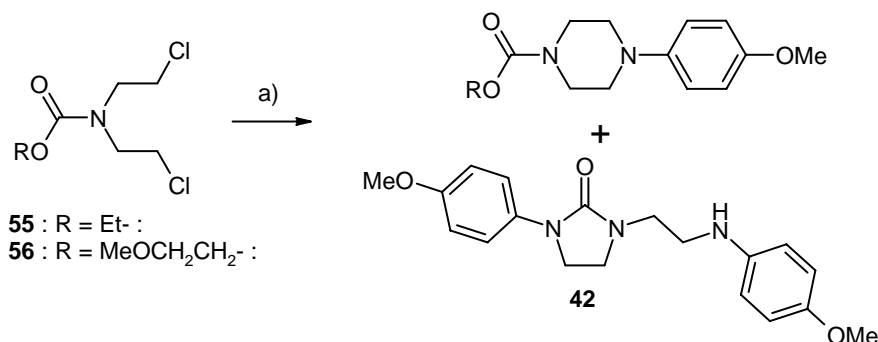
A systematic study of the reaction was planned to identify the determining factors in the reaction and to gain insight into the mechanism of cleavage.

Initially the reaction was compared to solution phase reactions with similar substrates under microwave conditions to elucidate whether performing the reaction on solid phase caused the imidazolidin-2-one formation (Scheme 40).



Scheme 40: a) chloroformate R=ethyl, 2-methoxyethyl, 1.2 equiv), K₂CO₃ (2 equiv), water, r.t., 2.5 h. b) 4-methoxyaniline (5 equiv), K₂CO₃ (2.5 equiv), KI (1 equiv), water, microwave, 120°C, 2400 s.

An experiment with resin-bound mustard **31** was run under the same conditions for comparison (Table 19).



| Entry | R- | Yield of 42 (%) | Piperazine compound formed | Yield of piperazine (%) |
|-------|----------------------|---------------------------|----------------------------------|----------------------------|
| 1 | ethyl | 4% ^{a,b} | 57 | - |
| 2 | 2-methoxyethyl | 10% | 58 | 11% |
| 3 | Versabeads VO 400 | 20% | 38 | 39% ^c |

Table 19: Results from the reaction of various mustard derivatives. ^a15% of 4-methoxyphenyl carbamic acid ethyl ester was also formed. ^b(4-methoxyphenyl) carbamic acid ethyl ester **59** (15% of theoretical yield) and a trace amount of **41** was also found. ^c Estimated from ¹³C gel-phase NMR spectrum.

The yield was markedly better when the resin-bound mustard **31** was employed, but lower than the yield from reactions with conventional heating under comparable conditions (Table 18, entry 2)

4.2.3 Microwave screening experiments

A series of experiments was run in order to obtain an initial feeling for which parameters were important for the reaction (Table 20).

| Entry | equiv. K ₂ CO ₃ | equiv. pyridine | equiv. iodide | Conditions | Yield 42 (%) | Cleavage ^a (%) |
|----------------|------------------------------------------|--------------------|------------------|---------------------------------------|------------------------|------------------------------|
| 1 | 2.5 | 0 | 1 | 5 ml H ₂ O; 120°C; 2400 s | 16 | 30 |
| 2 | 0 | 0 | 10 | 5 mL H ₂ O; 150°C; 3180 s | 4 | 21 |
| 3 ^b | 4 | 0 | 1 | 5 mL H ₂ O; 150°C; 3600 s | N/A | 30 |
| 4 | 0 | 5 | 1 | 5 mL H ₂ O; 150°C; 3180 s | trace | 42 |
| 5 | 0 | 5 | 0 | 5 mL H ₂ O; 150°C; 3180 s | trace | 50 |
| 6 | 0 | - ^d | 0 | 5 mL pyridine; 150°C; 3180 s | 4 | ^e |
| 7 | 2.5 | 0 | 1 | 5 mL H ₂ O; 80°C; 23 h | 29 | 55 |
| 8 | 2.5 | 0 | 1 | 10 mL H ₂ O; 150°C; 3180 s | 29 | 40 |

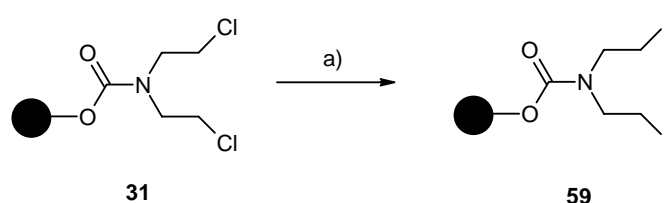
Table 20: a) 4-methoxyaniline (5 equiv), microwave heating. ^a Estimated from ¹³C gel-phase NMR spectrum. ^b Only 2 equivalents of 4-methoxyaniline were used. ^c No traceable yield. ^d Pyridine used as solvent ^e No visible cleavage by ¹³C gel-phase NMR.

The higher reaction temperatures seem to favour piperazine formation over cyclitative cleavage. An explanation could be that the increased reaction rates favours the intramolecular reaction over the intermolecular reaction. Another explanation could be that the hydrophobic interaction between the aniline molecules are lessened and the aniline is therefore more evenly distributed in the reaction mixture.

Because of the significantly lower yields of product obtained from the synthesis with microwave heating (Table 20) compared to those with conventional heating (table 18), it was decided to continue the investigation using conventional heating.

4.2.4 NMR-monitored experiments

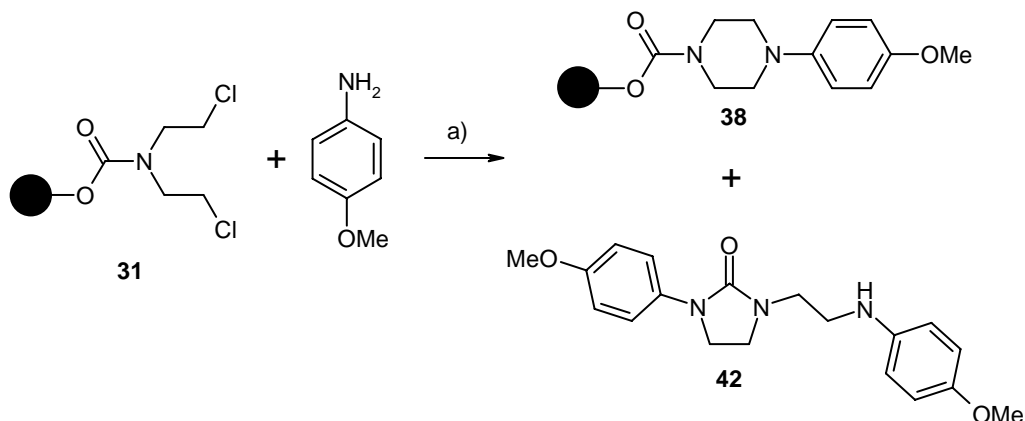
In an attempt to monitor the reaction in real time, resin and reagents were heated together in an NMR tube in the spectrometer at 80 °C, where ^{13}C spectra were obtained at regular intervals. When a reaction between the resin-bound mustard and 2 equivalents of potassium iodide (in the absence of an aniline) was performed in deuterated water, the iodo intermediate was detected as a peak appearing at approximately 3 ppm after 3 hrs. As a rough estimate, approximately 30 % of the alkyl chloride had been converted to the alkyl iodide. This indicates that chloride-iodide exchange occurs smoothly. Therefore, if an alkyl iodide peak is not observed in these reactions, it implies simply that the alkyl iodide has a short lifetime (Table 21).



| Entry | time (h) | Conversion (%) ^a |
|-------|----------|-----------------------------|
| 1 | 0 | 0 |
| 2 | 3.5 | 6 |
| 3 | 5.5 | 15 |
| 4 | 9 | 22 |
| 5 | 13.5 | 31 |

Table 21: Reaction between **31** and iodide in an NMR tube. a) KI (2 equiv), D₂O, 80 °C. ^aConversion estimated from cutting and weighing of peaks at 3 ppm (-CH₂I) and 41 ppm (-CH₂Cl).

The reaction between resin bound mustard and aniline was not performed under these conditions due to practical problems with the mixing in the NMR tube. Instead, an experiment was performed in the usual fashion, and samples were removed at regular intervals, immediately quenched through cooling and removal of solvent, and the resultant resin samples were then prepared for ^{13}C gel-phase NMR (Scheme 41).

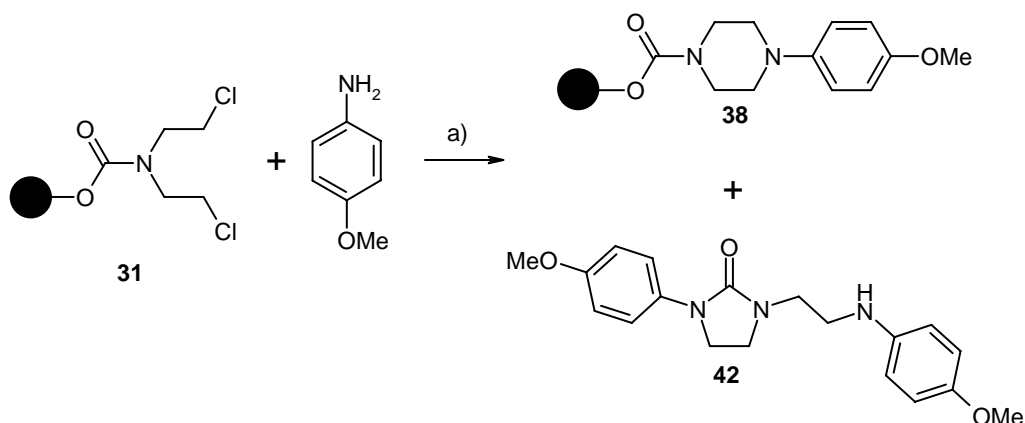


Scheme 41: Reaction between 4-methoxyaniline and **31** monitored by NMR. a) 4-methoxyaniline (5 equiv), K_2CO_3 (2.5 equiv), KI (2 equiv), 80 °C, 24 h.

Unfortunately only reactant and product were visible in the spectra, as most of the possible intermediates give peaks in the same area as the reactant and product, but some information could be extracted from the experiment. By comparing the peaks at 64 ppm and 61 ppm it was discovered that the reaction had reached about 50 % cleavage after 3.5 h and were close to completion after 7 hrs, meaning that overnight reaction would most likely been sufficient for a realistic maximum yield. It could also be assumed that the iodo intermediates were relatively short-lived when base was present as no $-CH_2I$ peak was visible at 3.5 ppm.

4.2.5 Parallel experiments at different temperatures

To identify the determining parameters in the reaction a series of experiments at three different temperatures were set up using Design of Experiments (table 22, 23 and 24).

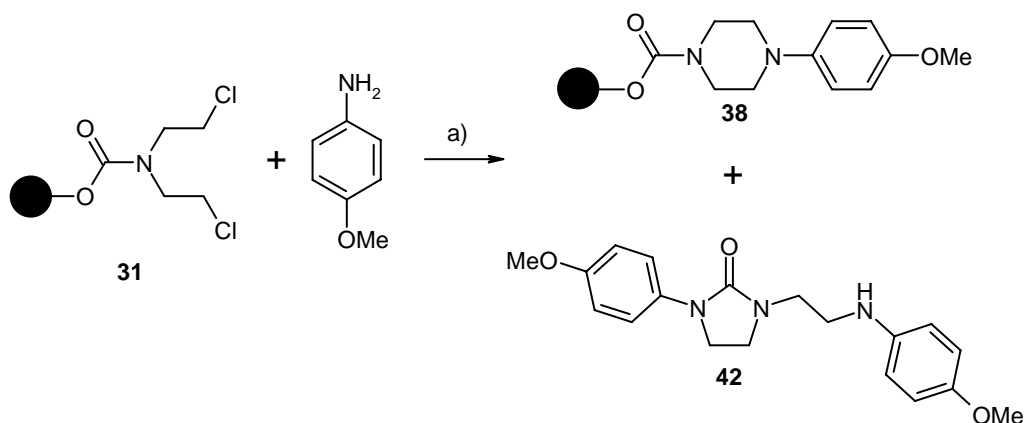


| Entry | equiv K ₂ CO ₃ | equiv KI | time (h) | Yield of 42 (%) ^a | Cleavage (%) ^b |
|-------|--------------------------------------|----------|-----------|----------------------------------------|---------------------------|
| 1 | 2.5 | 2 | 23 h | 38 | 68 |
| 2 | 2.5 | 1 | 23 h | 31 | - ^c |
| 3 | 2.5 | 0 | 23 h | 31 | 58 |
| 4 | 1.25 | 2 | overnight | 39 | 65 |
| 5 | 1.25 | 1 | 23 h | 28 | 71 |
| 6 | 1.25 | 0 | overnight | 38 | 74 |
| 7 | 0 | 2 | overnight | 5 | ^c |
| 8 | 0 | 1 | overnight | 5 | ^c |
| 9 | 0 | 0 | overnight | 16 | ^c |

Table 22: Screening reaction between **31** and 4-methoxyaniline at 80 °C. a) 4-methoxyaniline (5 equiv), K₂CO₃, KI, water. ^aIsolated yield of **42** after purification with FlashMaster (based on initial Versabeads loading). ^bEstimated from ¹³C gel-phase NMR. ^cNo cleavage detected.

The reactions were initially run for 23 hours, but experiments showed that full reaction could be reached overnight (15-17 h), so this was chosen due to time constraints. The general picture from the reaction at 80 °C was that yields were high when base was present, but dropped dramatically when only iodide was present (Table 22).

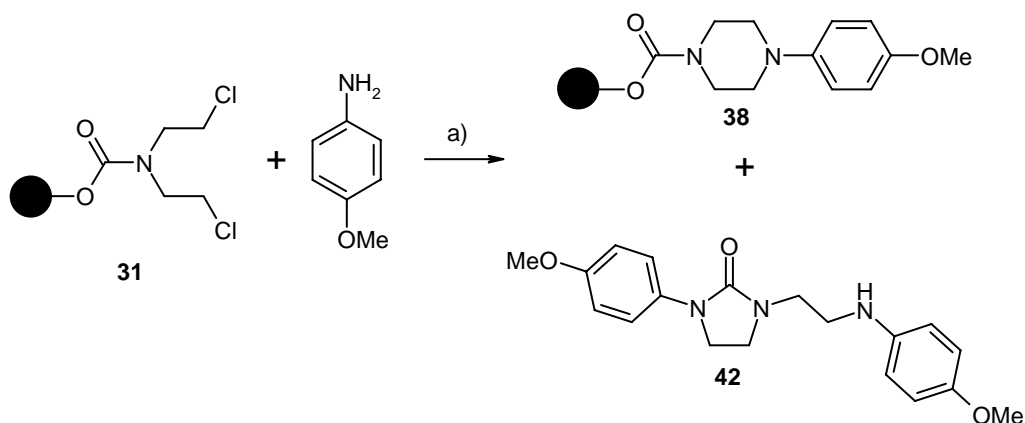
When the reaction was run at 60 °C yields were generally lower and the reactions did not run to completion overnight (peak from -CH₂Cl still visible in the ¹³C gel phase NMR spectrum) (Table 23). The reason might be that 4-methoxyaniline (m.p. = 57-58°C) was only partly melted at this low temperature and slow in diffusing into the beads. This is consistent with the fact that significant cleavage from resin was still observed, but no phenyl-containing cleavage product was isolated. Therefore, the hydrolytic cleavage without aniline involvement was significant compared to aniline addition.



| Entry | equiv K ₂ CO ₃ | equiv KI | time | Yield of 42 (%) ^a | Conversion to 38 (%) ^b |
|-------|-----------------------------------------|----------|-----------|----------------------------------------|---------------------------------------------|
| 1 | 2.5 | 2 | overnight | 4 | - ^c |
| 2 | 2.5 | 1 | overnight | 15 | - ^c |
| 3 | 2.5 | 0 | overnight | 10 | 23 |
| 4 | 1.25 | 2 | overnight | 10 | low |
| 5 | 1.25 | 1 | overnight | 14 | 23 |
| 6 | 1.25 | 0 | overnight | 5 | 32 |
| 7 | 0 | 2 | overnight | 6 | 31 |
| 8 | 0 | 1 | overnight | 8 | - ^c |
| 9 | 0 | 0 | overnight | 4 | 35 |

Table 23: Screening reaction between **31** and 4-methoxyaniline at 60 °C. a) 4-methoxyaniline (5 equiv), K₂CO₃, KI, water. ^aIsolated yield of **37** after purification with FlashMaster. ^bEstimated from ¹³C gel-phase NMR. ^cNot estimated due to poor spectral resolution.

More surprising, the yields at 100 °C are generally slightly lower than seen at 80 °C (Table 24). As the extent of cleavage from resin was still about the same, it is possible that the higher temperature favours hydrolysis. This was consistent with the fact that more hydrolysis product seemed to be formed (This was estimated from the printouts from the FlashMaster, which recorded the UV absorption of the eluent). Otherwise the yields showed the same pattern as for 80 °C, similar for all reactions with base, and dropping dramatically without base.



| Entry | equiv K_2CO_3 | equiv KI | time | Yield of 42 (%) ^a | Cleavage from resin (%) ^b |
|-------|-------------------------------|----------|-----------|----------------------------------------|--------------------------------------------|
| 1 | 2.5 | 2 | overnight | 27 | 63 |
| 2 | 2.5 | 1 | overnight | 34 | 68 |
| 3 | 2.5 | 0 | overnight | 25 | - |
| 4 | 1.25 | 2 | overnight | 29 | 65 |
| 5 | 1.25 | 1 | overnight | 29 | 68 |
| 6 | 1.25 | 0 | overnight | 25 | 70 |
| 7 | 0 | 2 | overnight | 2 | 27 |
| 8 | 0 | 1 | overnight | 4 | 48 |
| 9 | 0 | 0 | overnight | 15 | |

Table 24: Screening reaction between **31** and 4-methoxyaniline at 100 °C. a) 4-methoxyaniline (5 equiv), K_2CO_3 , KI, water. ^aIsolated yield of **42** after purification with FlashMaster. ^bEstimated from ^{13}C gel-phase NMR.

Analysis of the results with MODDE showed that the yield of imidazolidin-2-one **42** was independent of the iodide addition, but affected by the amount of base and the temperature. This is consistent with results from literature, where the piperazine formation has been shown to be favoured over the addition of a second aromatic amine molecule when no base was added.²⁴⁵

Most of the reactions yielded trace amounts of hydrolysis by-products, especially at 100 °C. Investigation of some of these by NMR showed that when base was present in the reaction mixture the hydrolysis product formed was almost exclusively the 1-(2-hydroxyethyl)-imidazolidin-2-one **53**, while the product formed in the absence of base (but in the presence of iodide) was the oxazolidin-2-one **41**. When neither base nor iodide was present a mixture of the two was isolated with the ratio of 1:3 **53/41**.

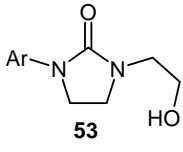
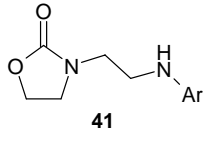
| Entry | equiv K ₂ CO ₃ | equiv KI | <div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center;">  <p>53</p> </div> <div style="margin: 0 10px;">•</div> <div style="text-align: center;">  <p>41</p> </div> </div> |
|-------|--------------------------------------|----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | 2.5 | 2 | 1:0.11 |
| 2 | 1.25 | 1 | 1:0.22 |
| 3 | 1.25 | 0 | 1:0.17 |
| 4 | 0 | 1 | 1:7 |
| 5 | 0 | 0 | 1:3 |

Table 25: Reaction temperature 80 °C. Estimated ratios by comparison between double doublets at 3.60 ppm (**41**) and 3.65 ppm (**53**)

4.3 Preliminary conclusions

The information gathered so far indicate that the yield of cyclic urea is dependent on the lifetime of the ionic intermediate **60** (Figure 23 and 24). When base is present the ionic intermediates are short-lived, meaning that the proportion of neutral intermediates is high. This means that an aniline molecule is more likely to undergo nucleophilic addition when it encounters an electrophile. It is also clear from the proportions of the byproducts that the imidazol-2-one ring formation is favoured over hydrolysis and oxazolidin-2-one ring formation under basic conditions, thereby disfavours the formation of hydrolysis byproducts. (Figures 22 and 23) In addition, hydrophobic clumping of the aniline (which would lead to higher local concentrations of the aniline) is also likely to be very important, since the cyclic urea is not observed in

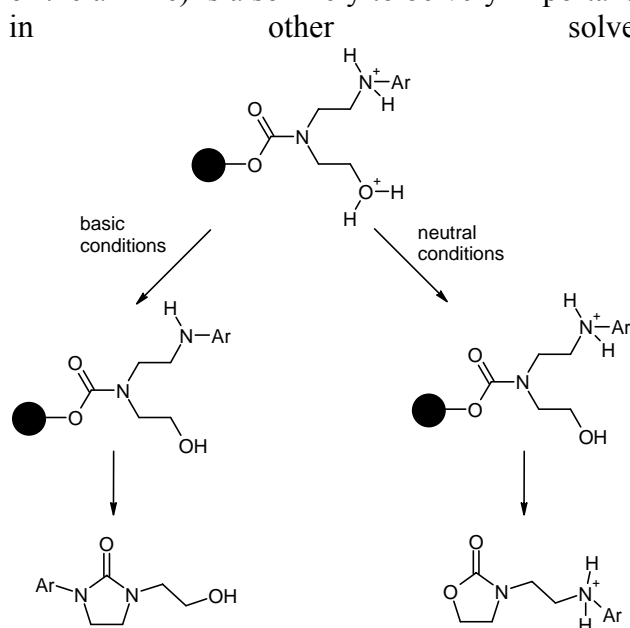


Figure 22: The proposed differently-favoured reaction pathways under neutral and basic conditions, judged by the proportion of byproducts (table 25). Under basic conditions neutralisation of both species are fast and the different nucleophilicities of the resin-bound species is the determining factor. When conditions are neutral/slightly basic the different acidity of the groups becomes a factor.

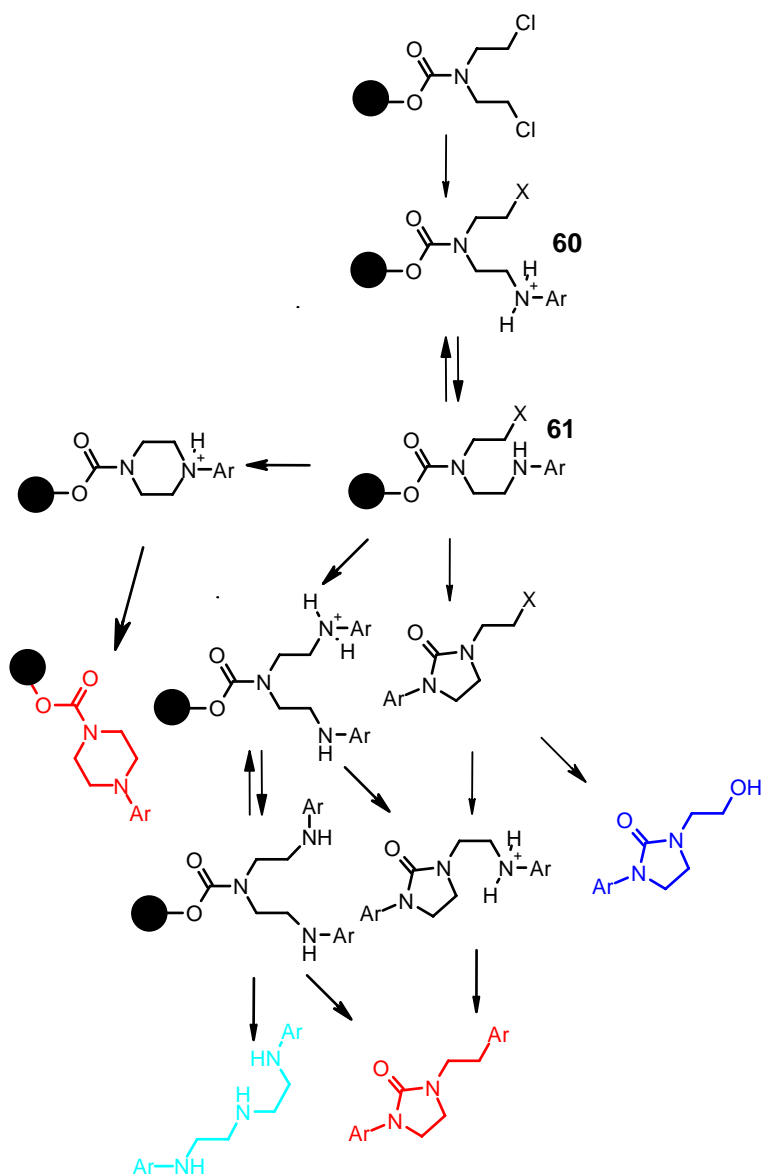


Figure 23: The proposed dominant reaction routes in the presence of additional base. The equilibrium between intermediates **60** and **61** is shifted towards **61**, and addition of more than one equivalent of aniline is therefore favoured.

When base is not present (except for the aniline) the neutralisation is slower, and the addition of anilines therefore disfavoured, as an aniline molecule is more likely to neutralize **60**, and less likely to add to an electrophile. Intramolecular ring closure to form the piperazine is therefore comparatively more favoured, which explains the higher proportion of piperazine ring closure (Figure 24).

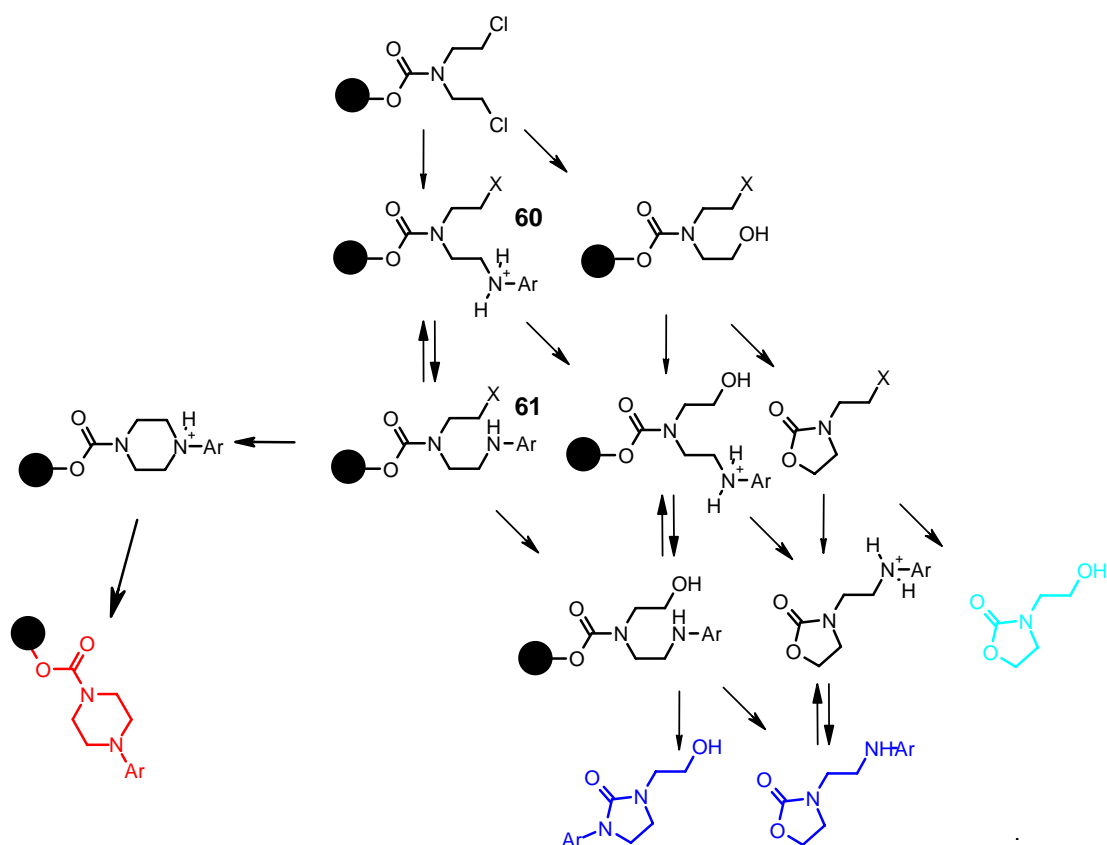


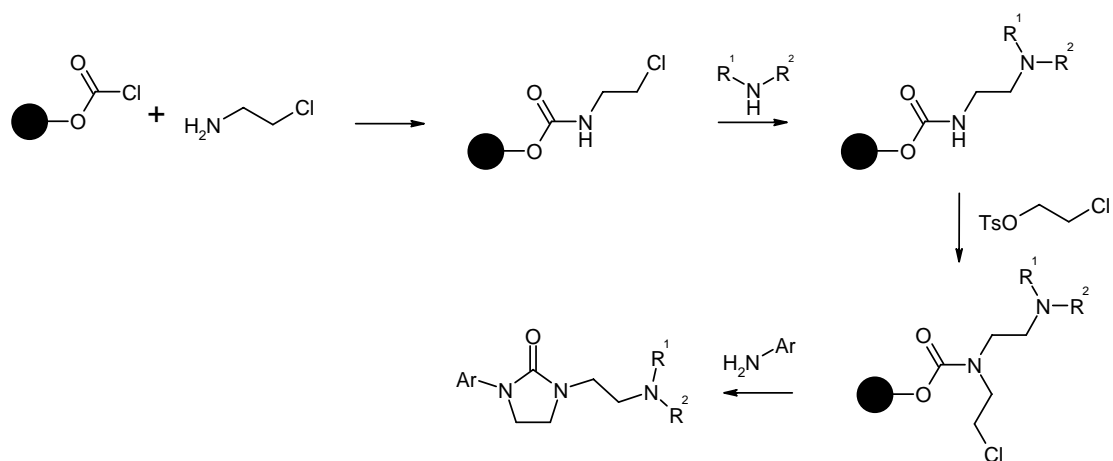
Figure 24: The proposed dominant reaction routes when no additional base is present. The long-lived ionic intermediate **60** disfavours a second nucleophilic addition of basic aniline.

It was clear that the formation of **42** would be favoured by the addition of more equivalents of aniline. This was confirmed by running a reaction with 10 equivalents of 4-methoxyaniline instead of 5 under the conditions employed in table 22, entry 1. A yield of 51 % of the imidazolidin-2-one **42** was obtained, with 60 % cleavage, indicating that the diaddition was greatly favoured over the hydrolysis reactions (Table 22, entry 1 had 68% cleavage).

4.4 Perspectives

This new method for synthesising imidazol-2-ones through cyclative cleavage in water holds potential for expansion and further investigation. More information on the mechanism, scope and limitations of the reaction can be gained by employing other anilines and amines in the reaction. Examining the reaction with fluoroanilines would be of special interest as this could potentially yield important mechanistic information through the use of ^{19}F spectroscopy.

The scope of the reaction would be greatly enhanced if it could be performed in a way so two different nucleophiles could be added to form the imidazolidin-2-one. One way of achieving this would be to substitute the carbamate with a dual electrophile (Scheme 42). Such additions have been performed on solid-phase bound carbamates before with good results.^{189, 197, 310, 311}



Scheme 42: Possible solid-phase route to differently substituted 1-arylimidazolidin-2-ones through cyclative cleavage.

5 Immobilization and catalytic effect of manganese porphyrin complexes

5.1 *Solid-phase reagents in organic synthesis*

Immobilizing the reagents on a solid support instead of the compound is another way of utilizing solid-support techniques in organic chemistry. The advantage of this approach is that both reagent and product are in solution, meaning that the traditional methods of reaction monitoring are available. The immobilized reagents can be easily removed and often regenerated and reused. If purification of the product is done with scavenger resins, the traditional advantages of solid-phase chemistry, easy use of excess and fast purification through filtration, can also be retained (Figure 25).

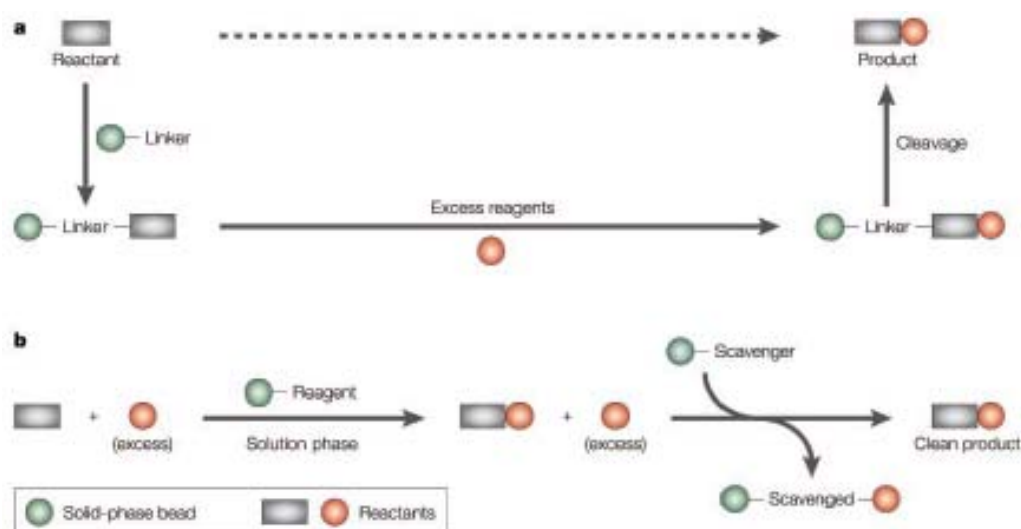


Figure 25: Traditional solid-phase synthesis (a) compared to solid-phase synthesis with immobilized reagents (b) ³¹⁶

The immobilization of reagents on solid phase and their subsequent use in synthesis and purification of organic compounds has been extensively reviewed over the last decade. ³¹²⁻³¹⁸

5.1.1 **Ley group research on solid-supported reagents and catalysts**

The Ley group at University of Cambridge has been one of the most active groups in the development of solid phase reagents and scavengers. In recent years the group has published papers on immobilized metal-based reagents, ^{319, 320} organic reagents ³²¹⁻³²³ and enzymes. ³²⁴ Several synthetic protocols based on solid phase reagents have been developed by the group, ³²⁵⁻³²⁸ as well as a number of total syntheses of natural products ^{329, 330} and drug compounds ³³¹ based on this kind of reagents.

Much of this work is aimed at developing automated or on-line synthesis procedures based on solid phase reagents, and the group has published several papers on this subject.³³²⁻³³⁵

5.2 *meso*-Tetraphenylmetalloporphyrins as catalysts for epoxidation

Metalloporphyrins are efficient catalysts for a number of oxidative transformations in nature, and a number of catalysts based on these structures have been developed, usually stabilized through *meso*-phenyl substitution (Figure 26)³³⁶⁻³³⁸ These catalysts have been shown to catalyze efficiently the epoxidation of alkenes under mild conditions with cheap oxidants such as bleach and hydrogen peroxide. Especially iron-, manganese- and ruthenium porphyrins have been used for this purpose^{336, 338-340} If chiral substituents are introduced, asymmetric epoxidation, a very important organic reaction, can be obtained with good e.e. values (50-80 %).³⁴¹

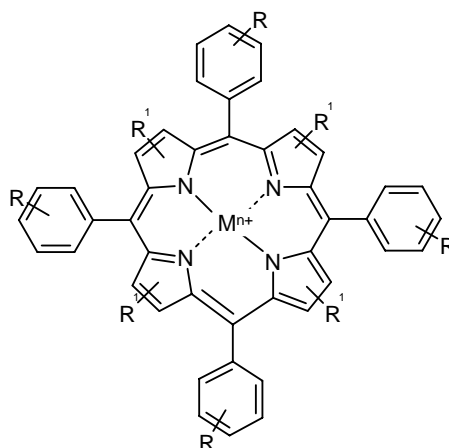


Figure 26: General structure for *meso*-tetraphenylmetalloporphyrin catalysts.

As porphyrins can be cumbersome and expensive to prepare, a number of studies have been carried out where metalloporphyrin catalysts are immobilized on a solid support.³⁴¹⁻³⁴⁸ Especially interesting in the context of Versabeads is the work of de Miguel *et al.*, who immobilized a manganese 5,10,15,20 tetraphenylporphyrin (TPP) analogue on Argogel and obtained good yields of various epoxides in aqueous phase employing sodium periodate as the oxidant (Table 26).³⁴⁹ Unfortunately the ArgoGel supported catalyst showed limited stability in these reactions and lost almost all activity after 3 cycles of styrene epoxidation. However, similar catalytic complex immobilized on soluble PEG support had proven stable for up to 6 cycles^{346, 350} and with the known chemical stability and good swelling properties of Versabeads O, it was believed that this support could prove superior to ArgoGel for this use.

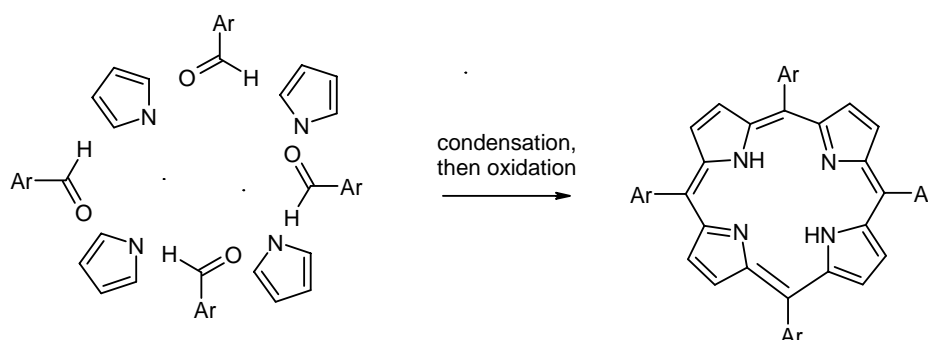
| Entry | Substrate | Yield of epoxide (%) ^a |
|-------|--------------------------|-----------------------------------|
| 1 | styrene | 80 |
| 2 | 1-methylstyrene | 51 |
| 3 | (Z)-cyclooctene | 98 |
| 4 | cyclohexene | 90 |
| 5 | bicyclo[2.2.1]hept-2-ene | 64 |

Table 26: Brule and de Miguel epoxidations of olefins with manganese TPP porphyrin supported covalently on ArgoGel.³⁴⁹ Conditions: Catalyst:imidazole:substrate:NaIO₄ molar ratio 1:10:23:46 in acetonitrile/water (2:1) at room temperature. ^aYield determined by GC (based on starting materials consumed and by-products present).

5.3 Synthesis and test of manganese meso-tetraphenylporphyrins immobilized on Versabeads.

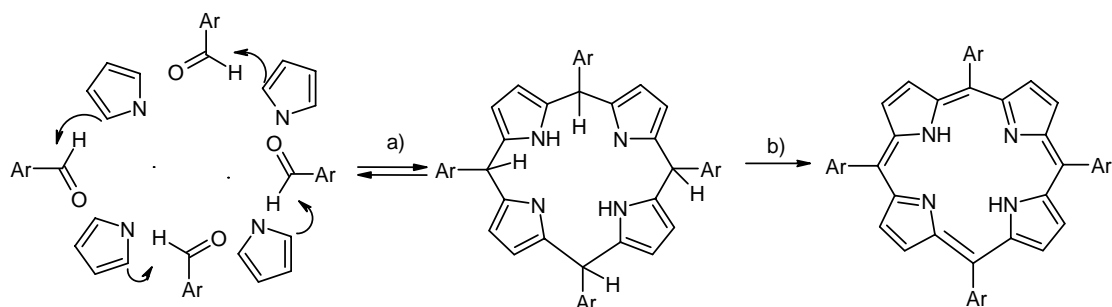
5.3.1 Porphyrin synthesis methods

Simple meso-phenylsubstituted porphyrins are usually made by condensation of pyrroles and aldehydes, followed by oxidation. The earliest syntheses of phenyl-substituted porphyrins were performed by heating the relevant benzaldehydes with pyrrole at reflux in propionic acid under aerobic conditions (Scheme 43). Unsymmetrical substitution patterns could be achieved by adding differently substituted benzaldehydes, thereby forming a statistical mixture of the possible products, which were then separated.³⁵⁴



Scheme 43: Synthesis of porphyrins by acid-mediated condensation (reflux in propionic acid in aerobic atmosphere). If differently substituted benzaldehydes are used a statistic mixture of the possible compounds are formed.³⁵⁴

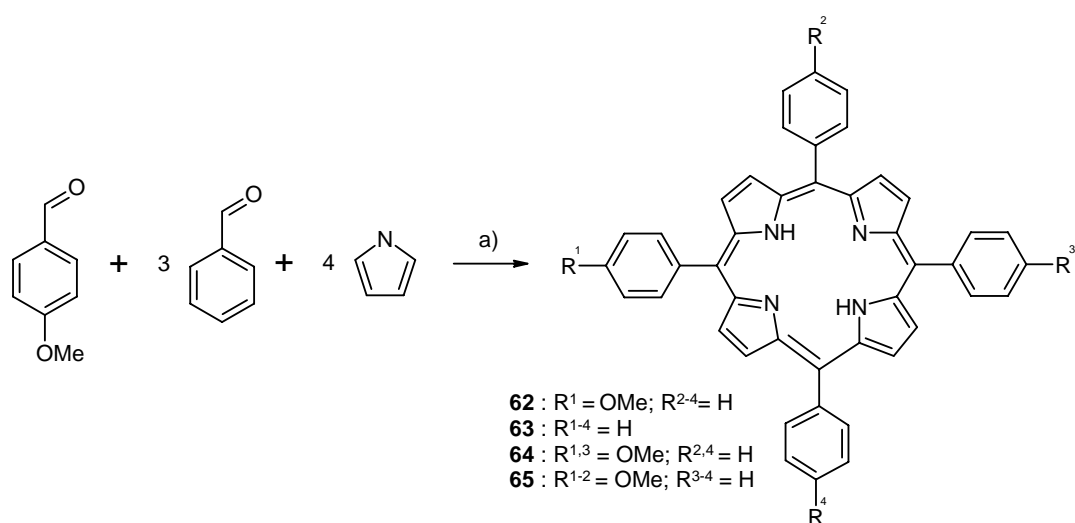
A more recently developed, gentler approach utilizes a Lewis acid mediated condensation between the substrates followed by oxidation.³⁵¹⁻³⁵³



Scheme 44: Lindsay *et al.*'s acid mediated synthesis of porphyrins³⁵¹ a) Acid, e.g. trifluoroacetic acid or boron trifluoride. b) mild oxidant, e.g. chloranil.

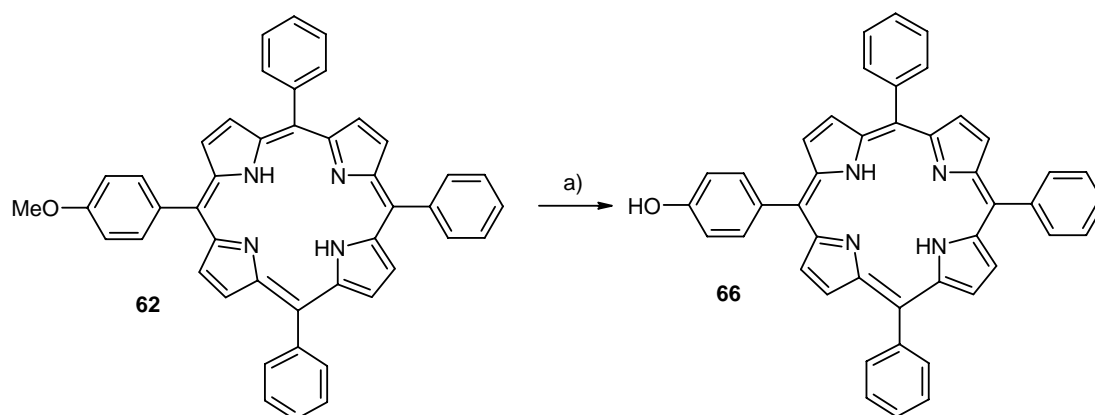
5.3.2 Synthesis of the catalytic complex

5-(4-methoxy)-10,15,20-tetraphenylporphyrin (**62**) was made by condensation of benzaldehyde, 4-methoxybenzaldehyde and pyrrole in refluxing propionic acid after the method developed by Little *et al.*³⁵⁴ The reaction itself was simple as the products crystallize from the acid upon cooling, but the separation of **62** from the byproducts, tetraphenylporphyrin (**63**) and particularly the small amount of dimethoxy products (**64** and **65**) required extensive column chromatography. The final yield of 2 % of **62** is very normal for synthesis of unsymmetrical porphyrins by this method (Scheme 45).



Scheme 45: Synthesis of **62** a) 4-methoxybenzaldehyde (1 equiv), benzaldehyde (3 equiv), distilled pyrrole (4 equiv), propionic acid, reflux, 3 h. The desired porphyrin was separated from the other products (**63-65**) by column chromatography. Yield 2 %.

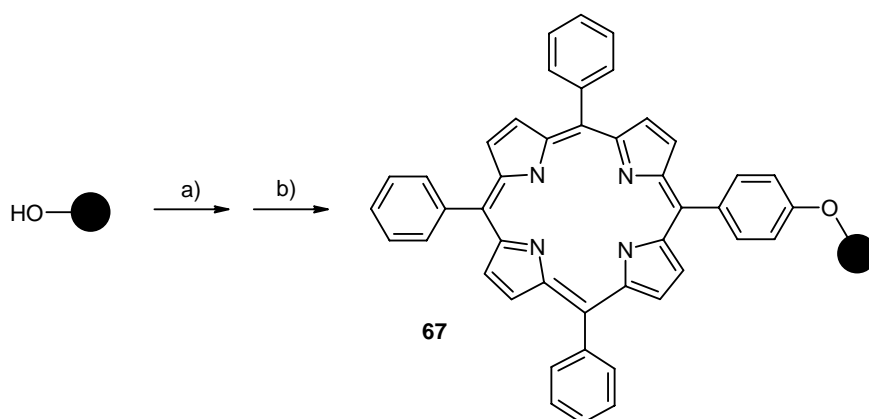
The compound 5-(4-hydroxy)-10,15,20-tetraphenylporphyrin (**66**) was made by cleavage of the methoxy group with BBr_3 (Scheme 46).^{355, 356}



Scheme 46: Deprotection of the hydroxyl group to form **66** a) BBr_3 (4.5 equiv), dichloromethane, $-78\text{ }^\circ\text{C} \rightarrow \text{r.t.}$, overnight. Yield 73% (Overall yield from starting materials 1.5 %).

In a later experiment an attempt was made to cleave the methoxy group before chromatographic separation of the products. The theory was that the increase in polarity difference between the porphyrins in the mixture would make chromatographic separation easier. Using this method, an overall yield of 1.3 % was achieved, and chromatographic separation was better and less time-consuming.

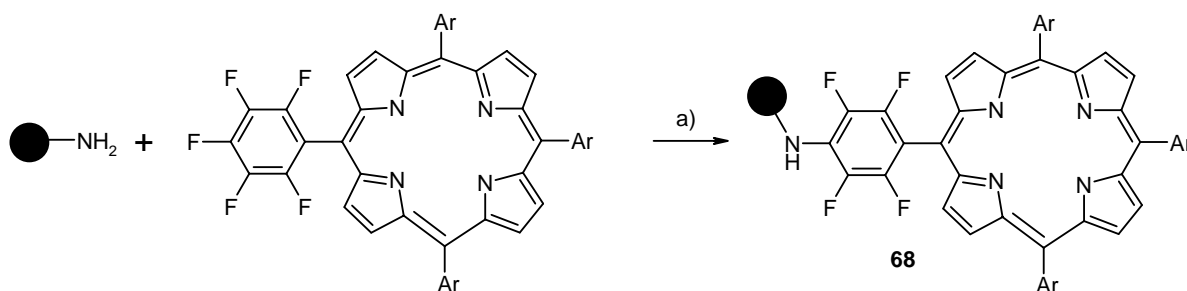
66 was attached to Versabeads through mesylation and nucleophilic addition, thereby forming the complex **67** (Scheme 47).⁶³



Scheme 47: Immobilization of **66** on Versabeads O a) Mesyl chloride (20 equiv), pyridine (84 equiv), DCM, r.t., 1.5 h, repeated. b) **66** (1.3 equiv), NaOH (1.1 equiv), DMF, $90\text{ }^\circ\text{C}$ overnight. Yield 70% (Estimated from CHN and Weight gain)

Another resin-bound porphyrin complex was made through addition of commercially available meso- Tetra(pentafluorophenyl)-porphyrin (TPFPP) to Versabeads A through nucleophilic addition in dimethyl formamide (Scheme 48).³⁵⁷ It is known that

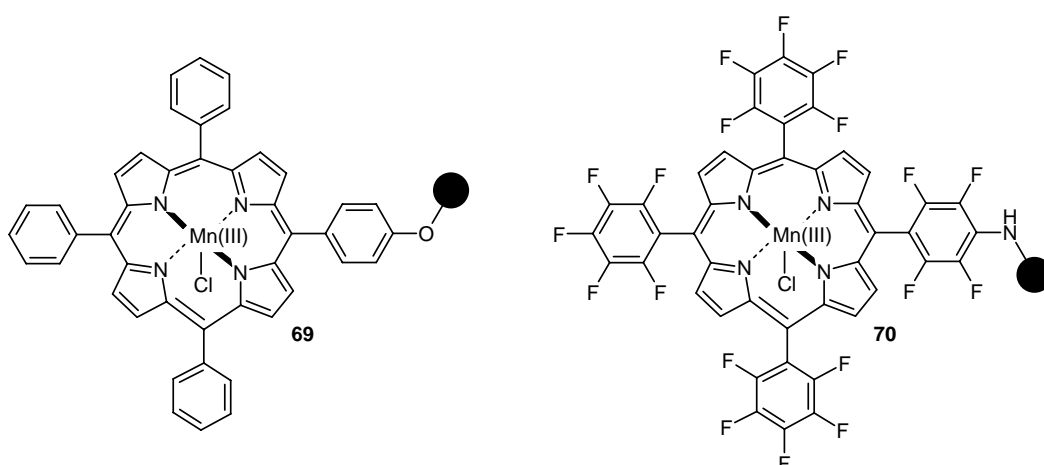
the reactivity of tetraphenylporphyrin complexes in oxidation reactions can be increased by having electron withdrawing groups on the phenyl rings.³³⁶



Scheme 48: Immobilisation of 5,10,15,20 – meso tetra(pentafluorophenyl)porphyrin (TPFPP) on Versabeads A800 (PEGA) to form complex **68** (Ar = C₆F₅-). a) TPFPP (1.4 equiv), DIPEA (1.4 equiv), DMF, 110 °C, overnight.

The immobilized porphyrins were metallated with Mn under the conditions used by de Miguel *et al.* (2h reflux in dimethyl formamide with excess MnCl₂*4H₂O)³⁴⁹ to give the catalytic complexes **69** and **70**. The metal content of the resins were determined by AAS. Resin samples were dissolved in warm nitric acid and diluted, after which the concentration was determined by evaporating the samples in an acetylene/oxygen flame and comparing it to standards.

From the described methods several batches of **69** and **70** were made, with mixed results (Table 27). The differences might be attributed to pollution with oxygen which might have oxidized manganese (II) to a state unavailable for the porphyrins (reference state rigorous anhydrous and anaerobic conditions)

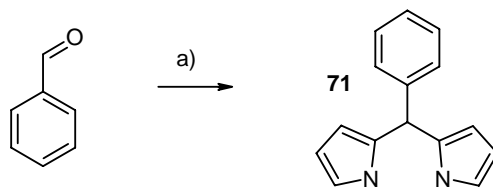


| entry | Catalyst made | theoretical max. loading (mmol/g) | AAS loading (mmol/g) | Yield (%) |
|-------|---------------|-----------------------------------------|-------------------------|--------------|
| 1 | 69 | 0.8 | 0.9 | 100 |
| 2 | 69 | 0.8 | 0.2 | 25 |
| 3 | 70 | 0.26 | 0.08 | 30 |
| 4 | 69 | 0.26 | 0.03 | 11 |
| 5 | 69 | 0.8 | 0.29 | 37 |
| 6 | 70 | 0.26 | 0.05/0.06 | 20 |

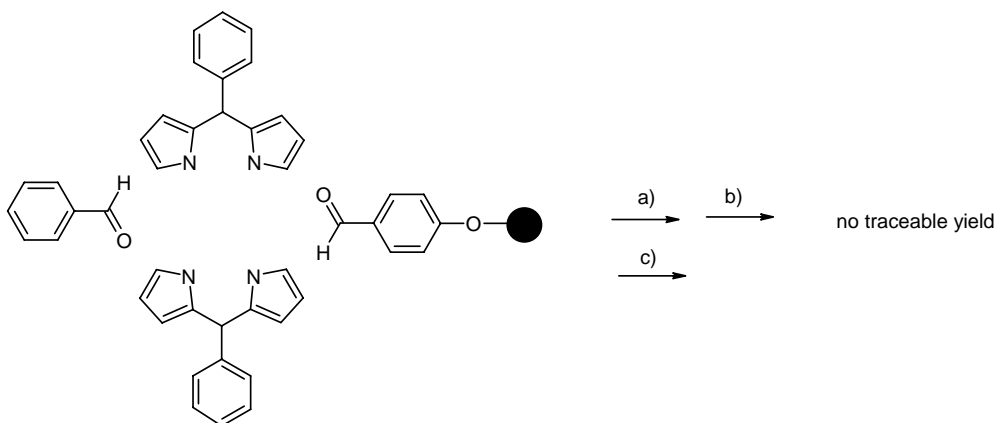
Table 27: Determination of the metal content in the various batches of catalytic complexes **69** and **70** by AAS

5.3.3 Attempted synthesis of porphyrin directly on solid phase

Earlier work has examined the synthesis of tetraphenylporphyrins directly on resin from a resin-bound aldehyde.^{358, 359} If the porphyrin could be synthesised directly on resin it could potentially avoid the cumbersome chromatographic separation of the porphyrins. An attempt was made to condense the porphyrins directly on resin using immobilised 4-hydroxybenzaldehyde.⁶³ As the propionic acid route produced huge amounts of polymeric impurities which might be trapped in resin, it was decided to try the milder Lewis acid mediated condensation of dipyrrolephenyl, followed by oxidation instead. Meso-phenyldipyrromethane **71** was produced in 53% yield (Scheme 49), but subsequent attempts to condense this compound with immobilized 4-hydroxybenzaldehyde (**26**) and benzaldehyde (Scheme 50) did not produce any of the characteristic bands in the IR spectrum. The reason might be that the condensation of benzaldehyde and polymerization was too favoured, compared to diffusion into the beads and reaction with the resin-bound aldehydes.



Scheme 49: Synthesis of meso-phenyldipyrromethane **71** a) Trifluoroacetic acid (cat.), pyrrole, r.t., 50 min.



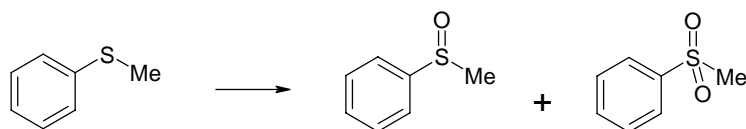
Scheme 50: Attempted synthesis of porphyrins directly on resin. a) **71** (4 equiv), benzaldehyde (4 equiv), trifluoroacetic acid (1 equiv), dichloromethane, r.t., 2 h b) 2,3-dichloro-5,6-dicyanoquinoline (6 equiv) c) **71** (3 equiv), benzaldehyde (1.5 equiv), boron trifluoride etherate (1.2 equiv), DCM, r.t., 2 h.

Recently Yang *et al* has succeeded in making simple porphyrin on polystyrene through the propionic acid route, followed by oxidation with 2,3 dichloro-5,6-dicyanoquinoline.³⁶⁰

5.3.4 Test reactions

5.3.4.1 Sulphide oxidation

Due to the carcinogenic nature of epoxides the oxidation of alkenes was not a feasible test reaction for the catalysts due to administrative reasons. Instead the oxidation of thioanisole to sulfoxide with *tert*-butyl hydroperoxide was chosen as a test case for the catalyst. Oxidation to sulfoxides has previously been used in investigation of the catalytic properties of iron porphyrin complexes in water.^{347, 361} *tert*-Butyl hydroperoxide has been reported to oxidize sulphides, in some cases with MnO₄ as co-reactant,^{362, 363} but a blind test reaction with oxidant gave no oxidation of the sulphide.



| Entry | substrate ^a : oxidant ^b : imidazole (mmol/equiv) | Catalyst (mmol) | Other additives ^c | Solvent ^d (mL:mL) | Other conditions ^e |
|-------|---------------------------------------------------------------------------------|-----------------------|----------------------------------------------------------|---------------------------------|----------------------------------|
| 1 | 0.23 : 0.44 : 0.1/ 9 : 18 : 4 | none | 0.025 mmol MnCl ₂ *4H ₂ O | 4 : 2 | stirred |
| 2 | 0.23 : 0.44 : 0.1/ 85 : 163 : 37 | 69 (0.0027) | - | 4 : 2 | stirred |
| 3 | 0.23 : 2.2 : 0.1/ 9 : 90 : 4 | none | 0.025 mmol MnCl ₂ *4H ₂ O | 4 : 2 | stirred |
| 4 | 0.23 : 2.2 : 0.1/ 85 : 815 : 37 | 69 (0.0027) | - | 4 : 2 | stirred |
| 5 | 0.23 : 0.44 : 0.1/ 85 : 163 : 37 | 69 (0.0027) | - | 4 : 2 | shaken |
| 6 | 0.17 : 1.7 : 0.1/ 63 : 630 : 37 | 69 (0.0027) | - | 3 : 1.5 | stirred |
| 7 | 0.23 : 2.2 : 0.1/ 85 : 815 : 37 | 69 (0.0027) | 1 mmol 2,6-di- <i>tert</i> -butyl-4- methoxyphenol | 4 : 2 | shaken |
| 8 | 0.23 : 2.2 : 0.1/ 77 : 733 : 33 | 70 (0.003) | - | 4 : 2 | shaken |
| 9 | 0.23 : 2.2 : 0.1/ 85 : 815 : 37 | 69 (0.0027) | - | 2 : 1 | shaken |
| 10 | 0.23 : 2.2 : 0.1/ 85 : 815 : 37 | 69 (0.0027) | - | 4 : 2 | stirred ^g |
| 11 | 0.23 : 2.2 : 0.1/ 77 : 733 : 33 | 70 (0.003) | - | 4 : 2 | stirred ^{g,h} |
| 12 | 0.23 : 2.2 : 0.1/ - | - | Versabeads/Mn ⁱ | 4 : 2 | stirred ^g |
| 13 | 0.23 : 0.44 : 0.1/ 230 : 440 : 100 | 70 (0.001) | - | 4 : 2 | stirred ^{g,h} |
| 14 | 0.23 : 0.44 : 0.1/ 58 : 110 : 25 | 69 (0.004) | - | 4 : 2 | stirred ^{g,h} |

Table 28: Conditions for the test of **69** and **70** as catalysts in the oxidation of thioanisole.

^a thioanisole, added as a standard solution in acetonitrile. ^b *tert*-butyl hydroperoxide, added as commercially available 70 % aqueous solution. ^c All reactions contained 1,2-dichlorobenzene, which was used as an internal standard for GC monitoring. ^d acetonitrile/water ^e all reactions were performed at room temperature. ^f radical inhibitor. ^g catalyst protected in an Irori Kan™ and removed after 1 h. ^h catalyst reused under the same conditions. ⁱ Versabeads O treated with MnCl₂*4H₂O in dimethyl formamide at reflux

| Entry ^a | Times reused | GC conversion (%) ^b | | | | |
|--------------------|--------------|--------------------------------|-----|-----|-----|----------------------------------------------------|
| | | 15 min | 1 h | 2 h | 3 h | later |
| 1 | | - | - | 0 | - | 48 h : 8; 65 h : 3. |
| 2 | | 15 | 31 | 39 | 46 | 17 h : 52; 20 h : 54; 48 h : 56. |
| 3 | | - | 3 | - | - | 53 h : 19. |
| 4 | | 26 | 44 | 56 | - | 4 h : 68; 17 h : 80; 20 h : 81. ^d |
| 5 | | 20 | 24 | 32 | 36 | 24 h : 45; 29 h : 44. ^d |
| 6 | | 34 | 60 | 66 | 71 | 20 h : 86; 28 h : 87. |
| 7 | | 11 | - | - | 49 | 5 h : 59; 24 h : 77; 48 h : 70. ^d |
| 8 | | 60 | 69 | 71 | - | 4 h : 72; 5 h : 72. |
| 9 | | 34 | 56 | 67 | 73 | 4 h : 77; 5 h : 77; 7 h : 80. |
| 10 | | 17 | 35 | 46 | 54 | 4 h : 61. |
| | 1 | 1 | 14 | 23 | 19 | 4 h : 15; 7 h : 28. |
| 11 | | 55 | 77 | - | 82 | 5 h : 84; 24 h : 85. ^d |
| | 1 | - | 41 | | - | 4 h : 65; 6 h : 72; 24 h : 77. |
| | 2 | | 5 | - | 9 | 4 h : 13; 24 h : 37. ^d |
| 12 | | - | - | 0 | - | 24 h : 0.1. |
| 13 | | 30 | 48 | 52 | - | 5 h : 60. |
| | 1 | 6 | 16 | 21 | 25 | - |
| | 2 | 4 | 12 | 9 | 13 | - |
| | 3 | 4 | 10 | 18 | - | 72 h : 32. |
| | 4 | - | - | 10 | - | - |
| | 5 | - | 3 | 5 | - | 5 h : 8. |
| 14 | | 18 | 33 | - | 41 | 9 h : 47. |
| | 1 | - | 0.5 | - | - | - |

Table 29: Results from the use of **69** and **70** in the oxidation of thioanisole as described in table 28. ^aEntry numbers corresponds to entries in table 28. ^bGC (Program: 60 °C, 3 min; 8 °C/min until 160 °C). Conversion measured as disappearance of starting material relative to 1,2-dichloromethane. ^cCatalyst removed after 1 h. ^dMn content in solution determined by AAS: Entry 4 : 0.58 µmol (22 %); entry 5: 0.86 µmol (35 %); Entry 7: 0.02 µmol (1 %); entry 11, first run: 1.5 µmol (50 %); entry 11, second reuse: 0.75 µmol.(25 %).

Reactions were monitored by the use of GC with 1,2-dichlorobenzene as an internal standard. A graph over catalyst activity (Figure 27) reveals that the first experiments) showed that conversion and rate depended on oxidant concentration and method of agitation, as stirring gave faster reaction rate and larger conversion than shaking ((Entry 2, 4 and 5). An increased catalyst: substrate ratio (Entry 6) gave a higher rate initially as did an increase in substrate concentration (Entry 9).

In all reactions catalyst seemed to be leaching into solution, judged by the rapid colouring of the reaction solution after addition of the oxidant. Furthermore the catalyst beads were physically broken down during the course of the reaction. This was initially believed to be the result of mechanical stress from the magnetic stirring, but the employment of shaking as an agitation method, and later the use of Irori kans™³⁶⁴ for bead protection did not prevent breakdown and leaching. On the contrary, upon removal of the Irori kan™ with the catalyst after 1h of reaction it was demonstrated that the reaction continued without the catalyst. Reuse of the catalyst showed that the catalyst had lost significant activity after the first reaction. (Table 29, entry 10) Subsequent AAS analysis of some of the reaction solutions detected the presence of a significant amount of Mn in the solution.

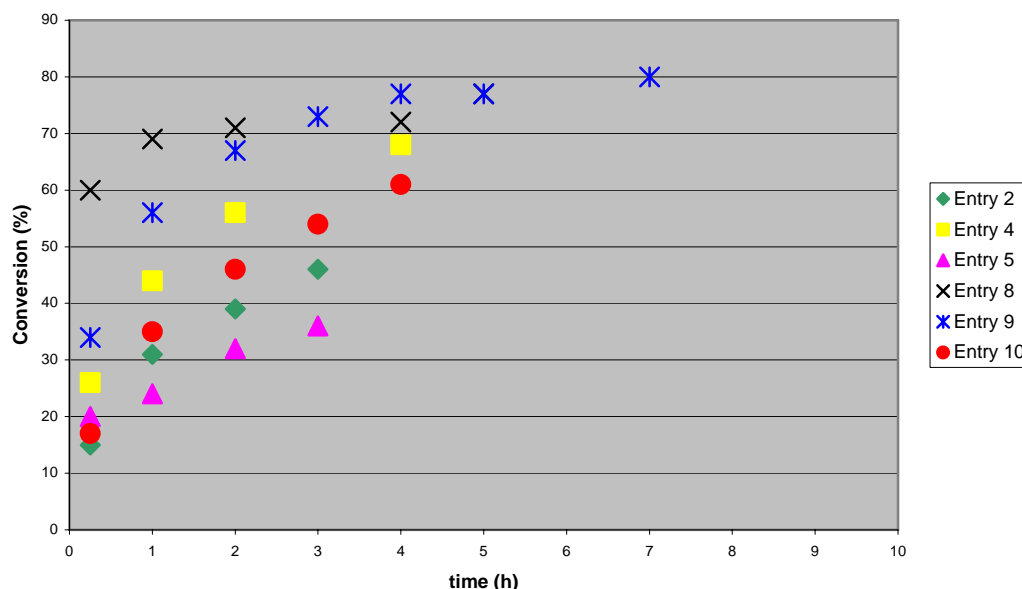


Figure 27: A comparison of the initial activities of catalysts **69** and **70** under various conditions. Not surprising an increased amount of oxidant leads to higher reaction rate (Entry 2 and 4), and an increased concentration further improves the rate (Entry 9) Note the differences between reactions with stirring (Entry 4), shaking (Entry 5) and stirring with catalyst in Irori kan™ (Entry 10). Also note the high initial activity (and fast deactivation) of **70** (entry 8) compared to **69** (Entry 4).

It was suspected that the catalyst might not have been properly attached to the resin before reaction, but an experiment with Mn adsorbed to SPOCC had no catalytic effect in reaction (Entry 12) and when porphyrin was adsorbed to resin (as opposed to covalently attached) to the beads were visibly different in colour and IR spectrum from **67**. An experiment with non-metallated porphyrin in a reaction solution proved that **67** was stable to reaction conditions, and that the leaching and breakdown of the beads most likely was caused by chemical instability towards the catalyst itself.

Catalyst breakdown and deactivation might be attributed to the formation of highly active radical intermediates, involving Mn(IV) and Mn(V). The formation of these can be prevented by adding a radical inhibitor to the reaction according to a study performed by Serra *et al.*³⁶⁵ In one experiment the radical inhibitor 2,6-di-*tert*-butyl-4-methoxyphenol was added to the reaction mixture, which resulted in increased yield and conversion (Table 29, Entry 7). The solution was again discoloured as the reaction progressed, but the Mn content found by AAS was remarkably low (1 % of theoretically possible compared to 33% for Entry 4). This might indicate that the highly active intermediates are partly responsible for the deactivation and breakdown. On the other hand the solution analyzed with AAS had a tendency to split in two phases, due to the high amount of organic material present, hence this result might not be considered conclusive.

A new batch of **69** was prepared (Table 27, entry 5). Upon use in the test reaction (Table 29, entry 10) with removal after 1 hour, this catalyst deactivated much faster than seen in earlier experiments with a catalyst with a lower loading, and showed virtually no activity in the second run (table 29, entry 14).

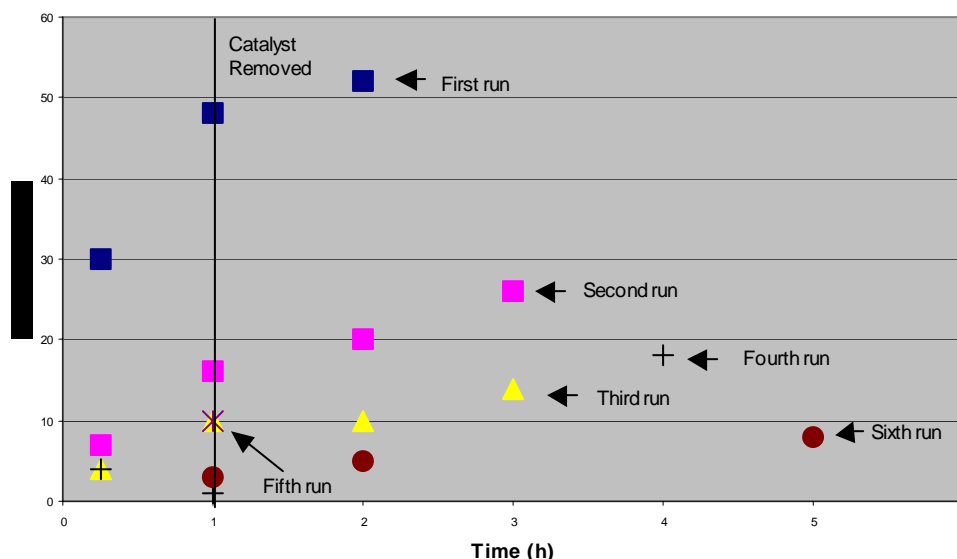


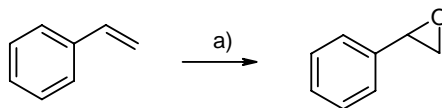
Figure 28: Reuse of catalyst **70** (Table 29, entry 13). The results indicate that an approximate steady state is reached between the third and the fifth run.

Experiments with **70** as catalyst showed a higher initial rate of oxidation than with **69**, but also a faster deactivation, which might indicate that the electron-deficient catalyst is more active, but also more prone to breaking down the resin. This could also be a question of Versabeads A being less stable than Versabeads O, as the former contains amide bonds (Table 29, entry 8).

A later experiment where catalyst **70** was reused six times showed that the activity seemed to stabilize after two reuses (at a level of approximately 20 % of the initial activity), again indicating that lower loading levels might be more stable. The catalyst was, however, completely destroyed after six runs (only traces of the beads were left in the Irori Kan™) (table 29, Entry 13 and figure 28).

5.3.4.2 Epoxidation

In an attempt to reproduce the de Miguel epoxidation of styrene with **70** and sodium periodate as oxidant (Scheme 51), 54% conversion was reached in 12 h (for comparison de Miguel *et al* reached 80%, but with a substrate/catalyst ration of 23:1). When the catalyst was removed the reaction continued, eventually reaching 84% conversion in 24 h. Upon reuse of the catalyst only 14% conversion was obtained.



Scheme 51: Epoxidation of styrene with **70** after the protocol of de Miguel *et al*. a) **70** (Irori Kan™): imidazole: styrene: NaIO₄ 1:39:73:153, 1,2-dichlorobenzene, acetonitrile/water (2:1), r.t. Conversion: 12 h: 54 %, 24 h: 84 %. Conversion upon reuse: 12 h: 14 %

5.4 Lanthanide porphyrin

Lanthanide salts are versatile catalysts in a number of organic transformations, for instance air- and water-stable Lewis acids.^{366 367, 368} Lanthanides supported on ion-exchange resin have been used to catalyse a number of reactions in water with good results.³⁶⁹

In a 1999 article by Wong *et al.* phenyl isocyanate was trimerised in 100% yield using 0.33 mol% of an Ytterbium tetraphenylporphyrin complex (Figure 29) as a Lewis acid catalyst under neat conditions. The catalyst showed remarkable stability, as it was reused two times without loss of activity.³⁷⁰

This prompted an investigation into whether an Yb porphyrin could be made on resin. Resin was treated with a large excess of YbCl₃*6H₂O at reflux in DMF, but there was no detectable change as measured by IR. As mono lanthanide porphyrins are known to be unstable towards acid,³⁷¹ it is possible that the HCl formed upon addition have prevented immobilization of the metal. Further experiments were not attempted.

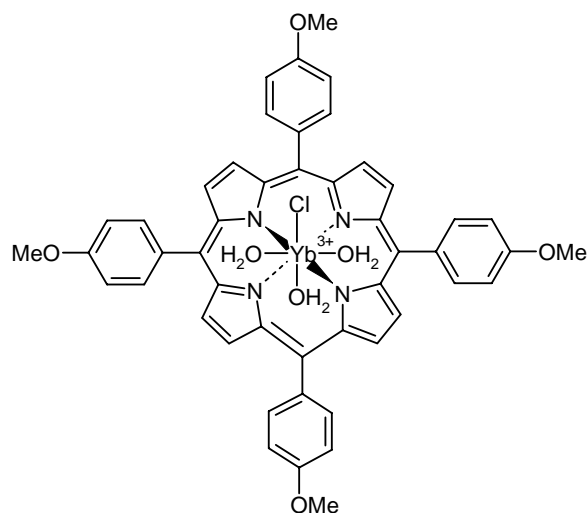


Figure 29: A stable Ytterbium porphyrin complex with catalytic properties by Wong *et al.*³⁷⁰

5.5 Perspectives

It was demonstrated that porphyrins can be immobilized and metallated on Versabeads, and analyzed successfully by AAS. The functionalised resin was apparently not stable to oxidative conditions, but the immobilized metalloporphyrins might still be useful in other metalloporphyrin-catalyzed reactions, such as cyclopropanation.

6 Conclusion

The present dissertation has investigated a number of possible uses for the SPOCC-based high-loading resin Versabeads, with special reference to the possibilities of performing chemistry in water and scaling-up of on-resin reactions to gram-scale. Furthermore, attempts were made to immobilize metalloporphyrin catalytic complexes on the resin.

6.1 *Large- scale synthesis on solid phase*

Two linkers based on known solid-phase chemistry were made on Versabeads and used in the synthesis of compounds of pharmaceutical interest: the acrylic acid based REM linker and the chloroformyl linker based on addition of phosgene. The chloroformyl linker was functionalized readily by the reaction of an amine salt in water. This reaction was used to synthesise a series of piperazines with different functionalities in good to fair overall yields and purities. The possibility of introducing additional functionalities through addition of nucleophiles in the cleavage step was briefly explored. This seems a promising concept, although further experiments did not yield any compound.

Likewise it was demonstrated that microwave heating could be used for rapid optimisation of reaction conditions on Versabeads similar to solution phase. The time-consuming reaction between mustard and anilines was optimized in a few days employing microwave heating. In the context of the desired acceleration of the initial drug development process this is a very interesting result

Using these optimized conditions a small organic molecule **45a** was synthesised on a 0.19 mol scale in good yield and excellent purity with only simple washing procedures as purification between steps.

The high-loading Versabeads could be reused without loss of activity. The question remains as to whether or not their physical properties change upon reuse, the extent of bead breakdown, and how to minimize it.

The REM linker was synthesised on resin and used for synthesis of difunctionalized piperazines. Again excellent compatibility between aqueous chemistry and Versabeads was demonstrated, as the reaction between allyl bromide and resin-bound piperazine took place with good yields. The good microwave properties of the resin was also documented, as evidenced from the good yields obtained by heating the reactions in this fashion. The REM linker based synthesis pathway was not explored in depth but appears promising.

The possibility of attaching a Wang linker to Versabeads was briefly explored and appeared to give a promising result. The easy access to attachment of various aromatic linkers based on phenol derivatives through direct nucleophilic addition or Mitsunobu reaction is a very useful result for further derivatization of the resin.

An important result was the discovery that cleavage of derivatized resin caused a distinct change in the ^{13}C gel-phase NMR spectrum, and the possibility to monitor reactions directly on the solid-phase through the use of short-time NMR experiments which made the solid-phase method more amenable for routine use as a tool in development chemistry.

It was shown that multi-step larger-scale solid phase synthesis could be easily accomplished in standard three-necked round-bottomed flasks using a glass tube equipped with a sinter to remove solvent from the reaction suspension, thereby avoiding the use of special solid-phase vessels for gram-scale solid-phase chemistry, which increases the practical use of this reaction pathway.

In short, it was demonstrated that a small molecule could be synthesised quickly and efficiently through solid-phase techniques using Versabeads.

6.2 Synthesis of imidazolidin-2-ones by cyclative cleavage

The surprising generation of an imidazolidin-2-one upon reaction between an aniline and the resin-bound mustard **31** in water led to a closer investigation of the mechanism and conditions behind the cyclative cleavage. Apparently the lifetime of the ionic intermediate **60** from the first addition of aniline is likely to be the determining factor for the ratio between cyclative cleavage and piperazine formation.

The cyclative cleavage reaction is very interesting, as the carbamate linker is otherwise very chemically stable, and it is quite possible that the favouring of this very interesting reaction is unique for hydrophilic resins like Versabeads. As described the reaction also takes place to some extent with mustard derivatives in aqueous solution, and this reaction has prompted further investigation at H. Lundbeck A/S.

6.3 Immobilization of metalloporphyrin catalysts on Versabeads

During the 6-month stay at the Ley group in Cambridge 5-(4-hydroxy)-10,15,20-*meso*tetraphenylporphyrin suitable for covalent linking to Versabeads was successfully synthesised and added to Versabeads O by known methods. 5,10,15,20-*meso* tetrapentafluorophenylporphyrin was immobilized successfully on Versabeads A, and both resin-bound porphyrins were complexed successfully with manganese. It was demonstrated that the catalytic complex hereby generated was an efficient catalyst towards sulphide oxidation and styrene epoxidation, but unfortunately the resins were unstable towards the catalytic complexes, as demonstrated by the removal of catalyst from the reaction solutions during reactions.

Although the resin thus proved not to be stable towards the oxidation catalysts these experiments have demonstrated the possibility for immobilizing metal complexes on Versabeads through nucleophilic addition and on-resin derivatization.

Attempts to synthesise the tetraphenyl porphyrin complex directly on resin from resin-bound 4-hydroxybenzaldehyde **26** proved unsuccessful. Addition of the lanthanide ytterbium to the resin was also unsuccessful.

7 Experimental

7.1 *Equipment used*

All chemicals and solvents were used as received unless otherwise stated. All reactions were run under nitrogen unless otherwise stated. All equivalents and yields in solid-phase reactions are based on initial Versabeads loading unless otherwise stated. Overnight reaction time is defined as 15-17 h. Solution-phase NMR were recorded on a Bruker 500 MHz spectrometer (Bruker 400 MHz for porphyrin experiments). ¹³C gel-phase NMR were recorded on a Bruker 250 MHz spectrometer using ordinary, disposable Norell NMR tubes. ¹H MAS NMR were performed at 11.75 Tesla on a Bruker Avance DRX-500 instrument. The MAS spin rate was 4 kHz. Automated flash chromatography was performed on an Argonaut Flash Master II using Isolute Flash Si II prepacked columns. Microwave heating was performed in closed vials on an Emrys Optimizer. LC/MS, UV and ELSD analysis were run in an integrated system. Key compounds were analyzed with a Waters Symmetry C18 column (4.6x30 mm, particle diameter 0.035 mm). MS were acquired using an Applied Biosystems API300 triple quadrupole mass spectrometer with Atmospheric Pressure Photoionization (APPI) ionsource. UV spectra were recorded with a Shimadzu SPD10A UV detector at 254 nm and ELSD with a Polymer Laboratories PL-ELS 2100 ELS-detector. ELSD analyzed screening was performed with a CDX85 ELSD detector. HPLC of crude products were taken on a Varian Star HPLC using a LiChrosorb RP-8 column (4x250 mm, particle diameter 0.005 mm). Eluent acetonitrile/water 50:50 buffered to pH=3 with a triethylamine/phosphate buffer. GC analysis was performed on a Hewlett Packard 5890 Series II instrument. Infrared spectra were taken on FT-IR instruments using attenuated total reflectance (ATR). Melting points were recorded on a Büchi B-540 melting point apparatus and appear uncorrected. CHN analyses were performed at the analytical department at H. Lundbeck A/S, halogen and sulphur analysis at the University of Vienna, Department of Physical Chemistry (Vienna, Austria).

7.2 The synthesis of Versabeads

(3-ethyloxethan-3-yl) triethylene glycolyl acetate (1)

(3-ethyloxethan-3-yl) triethylene glycol (201 g, 0.81 mol, 1 equiv) was slowly dissolved in pyridine (400 mL) on an ice bath. Acetic acid anhydride (200 mL, 216 g, 2.12 mol, 2.6 equiv) was added slowly with cooling, and the reaction was allowed to proceed overnight at room temperature. The reaction mixture was dissolved in ethyl acetate (1000 mL). The organic solution was washed with water (2 x 1000 mL) and brine (2 x 250 mL) and dried (anhyd magnesium sulphate). The solvent was removed in vacuo to give 166 g (71% yield) of **1** as a light yellow oil.

¹H-NMR (CDCl₃; 250 MHz): δ = 0.9 (3H, t, H1); 1.7 (2H, q, H2); 2.0 (3H, s, Ac-) 3.5-3.8 (12H, m, -(CH₂CH₂O)_n-); 4.1 (2H, m, H3) 4.2-4.5 (4H, m, oxethane ring)

(3-ethyloxethane-3-yl)methyl tosylate (2)

(3-ethyloxethane-3-yl)methanol (203 g, 1.75 mol, 1 equiv) was cooled to 0°C on a dry ice bath. An aqueous solution of sodium hydroxide (3 M, 700 mL, 2.1 mol, 1.2 equiv) was added followed by addition of a solution of tosyl chloride (398 g, 2.08 mol, 1.2 equiv) in THF (700 mL). The temperature was kept below 5°C. After addition the solution was allowed to stand for 3 h. NaCl was added until an organic phase separated. The organic phase was evaporated and the remains were dissolved in ethyl acetate (200 mL). This solution was washed with water (2 x 200 mL), saturated aqueous sodium bicarbonate (1 x 200 mL) and brine (1 x 200 mL), dried (anhyd magnesium sulphate) and evaporated.

To remove excess tosyl chloride the product was dissolved in ethyl acetate (250 mL) and washed with saturated aqueous sodium bicarbonate (1x200 mL) and 1 M aqueous sodium carbonate (2 x 200 mL). The organic phase was washed with brine (200 mL), dried (anhyd magnesium sulphate) and evaporated.

The product was dissolved in ethyl acetate (250 mL) then washed with 1 M aqueous ammonia (3 x 200 mL), dried (anhyd magnesium sulphate) and evaporated to give product **2**. Product contains 4.4 % (w/w) of p-toluenesulphonic acid as an impurity. Yield: 311 g (64%)

¹H-NMR: (CDCl₃; 250 MHz) δ = 0.7 (3H, t, H1); 1.7 (2H, q, H2); 2.3 (3H, s, Tosyl- + water) 4.1 (2H, s, H3); 4.2-4.3 (4H, m, oxethane ring); 7.3 (2H, d, Tosyl-) 7.8 (2H, d, Tosyl-)

Bis(3-ethyloxethan-3-yl)PEG-12 (3)

(3-ethyloxethan-3-yl) PEG-12 (333 g, 0.51 mol, 1 equiv) was slowly added to a suspension of potassium *tert*-butoxide (87 g, 0.78 mol, 1.5 equiv) in THF (200 mL) at room temperature. **2** (172 g, 0.64 mol, 1.2 equiv) was added slowly as a solution in THF (total volume 500 mL).

THF (1400 mL) was gradually added to the mixture over the next hour, to make it less viscous, and the reaction was allowed to stand overnight without stirring and then filtered. The filtrate was concentrated in vacuo and the residue was dissolved in

dichloromethane (500 mL). The organic phase was washed with water (2 x 500 mL), 1 M aqueous sodium carbonate (2 x 250 mL) and brine (2 x 250 mL), dried (anhydrous magnesium sulphate) and evaporated.

End weight: 257 g with 3% (w/w) of p-toluenesulphonic acid as an impurity. Yield 67 %

$^1\text{H-NMR}$ (500 MHz; CDCl_3): δ = 0.82 (6H, t, H1) 1.67 (4H, q, H2) 3.52 (2H, s, H3); 3.57 (56H, s, $-(\text{CH}_2\text{CH}_2\text{O})_n-$) 4.35 (8H; m; oxethane rings) 7.8 (TsOH impurity)

Polymerization process to form Versabeads.

1 (18 g, 25 mmol, 1 equiv) and **3** (5.8 g, 20 mmol, 0.8 equiv) was dissolved in acetonitrile (10 mL) with 1% surfactant (Polysurf 30). The solution was cooled to -20°C under Ar and boron trifluoride diethyletherate (0.6 mL ($\rho=1.120$), 0.71 g, 5 mmol, 0.2 equiv) was added. The solution was quickly transferred to silicon oil (600 mL) in a polymerization reactor. The suspension was stirred at 250 rpm at room temperature for 2 h and then left standing overnight.

The silicon oil suspension was filtered and the beads were washed successively with a hexane/heptane mixture, dichloromethane, tetrahydrofuran, methanol and water. Sieving of the beads yielded equal amounts of 120-80 μm beads and 80-40 μm beads.

IR = 1734 cm^{-1}

The beads were suspended in 4 M aqueous HCl and heated for 2 h at 60°C , and then washed repeatedly with water until the pH of the washing water was above 6, then dried.

IR showed no trace of the ester stretch at 1734 cm^{-1} .

Total yield 6.69 g

^{13}C gel phase NMR (62.5 MHz; CD_2Cl_2): δ = 73.4 ($-\underline{\text{CH}}_2\text{CH}_2\text{OH}$), 71.3 ($-(\underline{\text{CH}}_2\text{CH}_2\text{O})_n-$), 62.3 ($-\text{CH}_2\underline{\text{CH}}_2\text{OH}$), 44.1 (C1), 22.2 (C2), 8.3 (C3).

Loading by Fmoc – glycine method: 0.5-0.6 mmol/g \sim 25% of theory.

^{13}C gel phase NMR of Versabeads O400 (Batch 1050007) (62.5 MHz; CDCl_3): δ = 72.3 ($-\underline{\text{CH}}_2\text{CH}_2\text{OH}$), 70.3 ($-(\underline{\text{CH}}_2\text{CH}_2\text{O})_n-$), 61.3 ($-\text{CH}_2\underline{\text{CH}}_2\text{OH}$); 43.1/40.9 (C1) 23.0 (C2) 17.2(C3) 7.5 (-) (C4) (Appendix A - Spectrum 1)

Fmoc Glycine Loading measurement general method

Fmoc-glycine (3 equiv relative to supposed loading), methyl imidazole (6 equiv) and 2,4,6-mesitylenesulfonyl-3-nitro-1,2,4-triazolide (6 equiv) was dissolved in dry dichloromethane at room temperature. The solution was added to ca. 50 mg Versabeads and the suspension was left for 45 min. The resin was washed with dry dichloromethane and dry DMF and the coupling reaction was repeated. The suspension was washed with dry dichloromethane (6 x 5 mL); dry DMF (6 x 5 mL) and dry methanol (1 x 5 mL) then dried on lyophilizer overnight.

Samples (size 5-10 mg) were treated with 5.00 mL of piperidine in DMF (20% v/v). The UV absorbance of the resulting solution was measured at 290 nm and compared to standard solution.

7.3 Linker synthesis

7.3.1 Carbamate linker synthesis

7.3.1.1 Initial synthesis

Initial synthesis of chloroformyl linker 4 on Versabeads

Versabeads O400 (2.5 g, 1.25 mmol, 1 equiv) were suspended in dry dichloromethane (15 mL). Triphosgene (1 g, 3.4 mmol, 8 equiv) was added and the suspension was cooled on ice. After 20 min pyridine (0.25 mL ($\rho = 0.978$ g/mL), 0.24 g, 3.1 mmol, 2.5 equiv) was added slowly, the cooling bath was removed and the reaction was stirred at room temperature overnight. The resin was filtered, washed with DMF (5 x 5 mL) and dried.

IR = 1770 cm^{-1}

Cl elemental analysis: 1.08% ~ 0.30 mmol/g (65% yield)

Addition of nucleophile to form 5

Resin 4 (1 g, 0.3 mmol, 1 equiv (based on elemental analysis of 4)) was suspended in DMF (8 mL) *N*-benzyl-*N*-methylamine (645 μL ($\rho = 0.94$ g/mL), 0.61 g, 5.0 mmol, 17 equiv) was added to the suspension, followed by DIPEA (0.13 mL ($\rho = 0.74$ g/mL), 0.10 g, 0.77 mmol, 4 equiv). The reaction was shaken at room temperature overnight, filtered, washed with DMF (5 mL), DCM (5 mL) and ethanol (5 mL) and then dried, to give resin 5.

IR = 1705 cm^{-1}

^1H MAS NMR (500 MHz, CD_2Cl_2): 2.8 ppm ($-\text{NCH}_3$); 4.4 ppm ($\text{PhCH}_2\text{N}-$); 7.1-7.4 ppm (Ph-)

Proof of concept: Reaction of 4 with 4-fluoroaniline to yield 6

Versabeads O400 (0.51 g, 0.25 mmol, 1 equiv) was suspended in THF (3 mL) in a syringe. A solution of phosgene in toluene (20% w/w, 1.25 mL ($\rho = 0.935$ g/mL), 0.23 g, 2.3 mmol, 9 equiv) was added and the mixture was agitated at room temperature overnight.

The resin was washed with THF (3 x 5 mL), then suspended in a solution of 4-fluoroaniline (0.66 g, 6 mmol, 24 equiv) in THF (5 mL) and agitated by rotating for 6 h at room temperature.

The resin was filtered, washed with THF (3 x 5 mL), DCM (5 mL), methanol (5 mL), DCM (5 mL) and methanol (5 mL) and then dried.

^{13}C gel-phase NMR (62.5 MHz, CDCl_3): $\delta = 156$ ppm (C1); 153 ppm (C2); 135 ppm (C3); 120 ppm (C4); 115 ppm (C5).

^{19}F NMR (470 MHz, CDCl_3): -121 ppm

^1H MAS NMR (500 MHz, CD_2Cl_2) 7.4 ppm; 7.2 ppm; 7.1 ppm; 6.8 ppm (aromatic protons)

IR: 1732 cm^{-1}

Proof of concept: Reaction between Versabeads and 4-fluorophenyl isocyanate to form 6

Versabeads O400 (0.53 g, 0.27 mmol, 1 equiv) was suspended in a solution of 4-fluorophenyl isocyanate (0.49 g, 3.6 mmol, 13 equiv) in dichloromethane (3 mL). After 1 h at room temperature a catalytic amount of triethyl amine was added and the suspension was agitated for 20 h. The suspension was filtered and the resin was washed with DCM (6 x 5 mL), THF (6 x 5 mL) and methanol (2 x 5 mL) and then dried to give resin 6.

^{13}C gel-phase NMR (62.5 MHz, CDCl_3): δ = 156 (C1); 153 (C2); 135 (C3); 120 (C4); 115 (C5).

^{19}F NMR (470 MHz, CDCl_3): δ = - 121.

^1H MAS NMR (500 MHz, CD_2Cl_2): δ = 7.4, 7.2, 7.1, 6.8. (aromatic protons).

IR: 1732 cm^{-1}

7.3.1.2 Investigation of cleavage conditions

Initial synthesis of 7

Resin 4 (1.8 g, 1.2 mmol, 1 equiv) was suspended in a solution of 1-dimethylphenylpiperazine (3.1 g, 12 mmol, 10 equiv) and triethylamine (0.25 mL (ρ = 0.73 g/mL), 0.18 g, 1.8 mmol, 1.5 equiv) in THF (6 mL), and the suspension was agitated at room temperature overnight. The suspension was filtered and the resin was washed with THF (6 x 5 mL), DCM (3 x 5 mL) and methanol (2 x 5 mL), then dried to give resin 7.

^{13}C gel phase NMR (62.5 MHz, CD_2Cl_2): δ = 156.9 (C1); 143.4 (C2); 129.4 (C3); 128.6 (C4); 127.9 (C5); 76.7 (C6); 71.3 (framework); 65.3 ($\text{CH}_2\text{-CH}_2\text{OR}$); 52.4 (C7); 44.7 (C8) 24.0, 8.4 (framework).

^1H MAS NMR (500 MHz; CD_2Cl_2): δ = 0.9 (framework) 2.4 (H1); 3.5 (H2); 3.6 (framework); 4.3 (H3); 7.2 (H4); 7.3 (H5); 7.4 (H6);

IR: 1701 cm^{-1}

N analysis gave 2.6 % ~ 0.92 mmol compound/g (160 % of theoretical content)

7.3.1.3 Acid/base mediated cleavage

Initial attempts to cleave 1-diphenylpiperazine (8) from resin (table 4)

Trifluoroacetic acid/dichloromethane (entry 1)

Resin 7 (0.92 g, 0.48 mmol, 1 equiv) was suspended in a mixture of dichloromethane and trifluoroacetic acid (1:1, 5 mL) and agitated for 1 h at room temperature. The suspension was filtered and the resin was washed with dichloromethane (3 x 10 mL). The cleavage reaction was repeated. The combined filtrates were evaporated to give a crude yield of 0.01 g. (< 10%). CHN analysis: 1.1 % N

HBr/acetic acid (entry 2)

Resin **7** (0.88 g, 0.46 mmol, 1 equiv) was suspended in a mixture of concentrated hydrobromic acid (48 % (w/w), 3 mL) and glacial acetic acid (3 mL). The suspension was agitated at room temperature overnight. The suspension was filtered and the resin was washed with water (3 x 10 mL) and dichloromethane (3 x 10 mL) and then dried.

¹³C gel-phase NMR (62.5 MHz, CD₂Cl₂): δ = 156 (C1); 129 (C2/C3); 77.2 (C4); 71.3 (framework); 65.7 (CH₂CH₂OR); 52.4 (C5); 44.2 (C6) 24.0, 8.4 (framework).

CHN analysis: 2.4 % N

The filtrate from the washing was made basic with aqueous potassium hydroxide (20%) and extracted with dichloromethane (6 x 25 mL). The combined organic phases were dried and concentrated in vacuo. No detectable yield of compound by LC/MS.

LiOH/ethanol (Entry 3)

Resin **7** (0.16 g, 0.08 mmol, 1 equiv) was suspended in a solution of lithium hydroxide (1.5 mmol, 20 equiv) in water/ethanol (1:2) in an Emrys Process Vial (2.5 mL). The vial was sealed and the suspension was heated with microwaves (80 °C, 1.5 h). The suspension was filtered, and the resin was washed with water (3 x 10 mL) and dichloromethane (3 x 10 mL) and then dried

CHN: N analysis 2.4 %

HBr/Acetic acid/heat (Entry 4)

Resin **7** (0.13 g, 0.07 mmol, 1 equiv) was suspended in a mixture of hydrobromic acid (48% w/w, 0.75 mL) and acetic acid (0.75 mL) in an Emrys Process Vial (2.5 mL). The vial was sealed and the suspension was heated with microwaves (80 °C, 1.5 h). The suspension was filtered, and the resin was washed with water (3 x 10 mL) and dichloromethane (3 x 10 mL) and then dried.

CHN: N analysis 2.17 %

Trifluoroacetic acid/dichloromethane /heat (Entry 5)

Resin **7** (0.12 g, 0.06 mmol, 1 equiv) was suspended in a mixture of trifluoroacetic acid (0.75 mL) and dichloromethane (0.75 mL) in an Emrys Process Vial (2.5 mL). The vial was sealed and the suspension was heated with microwaves (80 °C, 1.5 h). The suspension was filtered, and the resin was washed with water (3 x 10 mL) and dichloromethane (3 x 10 mL) and then dried.

CHN: N analysis 2.38 %

Ammonia/methanol (Entry 6)

Resin **7** (1.2 g, 0.6 mmol, 1 equiv) was suspended in 4 mL of a solution of ammonia in methanol (4 M). The suspension was stirred at room temperature overnight.

LC/MS of the solution phase showed no compound.

The suspension was filtered, and the resin was washed with methanol (3 x 10 mL) then resuspended in a solution of ammonia in methanol (4 M, 4 mL) in an Emrys Process Vial (5 mL). The vial was sealed and the suspension was heated with microwaves (1.5 h, 60 °C). The suspension was filtered, and the resin was washed with ethanol (4 x 10 mL) then dried.

IR showed no change from the starting material.

KOH/ethanol (entry 7)

Resin **7** (0.8 g, 0.48 mmol, 1 equiv) was suspended in ethanol (2 mL) in an Emrys Process Vial (5 mL). Potassium hydroxide (0.14 g, 2.5 mmol, 5 equiv) was added, the vial was sealed and the suspension was heated with microwaves (150 °C, 2 h). The suspension was filtered, and the resin was washed with ethanol (3 x 10 mL); dichloromethane (3 x 10 mL) and ethanol (3 x 10 mL) and then dried.

IR of resin showed no carbonyl stretch (1701 cm^{-1})

^{13}C gel-phase NMR (62.5 MHz; CD_2Cl_2) showed none of the characteristic peaks from **7**

The filtrate was evaporated and the residue was purified with ion-exchange SCX-columns. End weight: 57 mg of **8** polluted with acetic acid from column activation. Yield, judged from ^1H NMR: 42-45%

^1H NMR (500 MHz, CDCl_3) δ = 1.94 (acetic acid); 2.35-2.45 (4 H, m, H1); 2.91-2.95 (4H, m, H2); 4.24 (1H, s, H3); 4.56-4.66 (m, NH); 7.16 (2H, dd, J = 6.8 Hz, H4); 7.26 (4H, dd, J = 6.8 Hz, H5); 7.40 (4H, d, J = 6.7 Hz, H6).

Attempted optimization of nucleophilic cleavage of **7**

Resin **7** (0.28 g, 0.24 mmol, 1 equiv) was suspended in solvent (1.5 mL) with base in Emrys Process Vials (5 mL) and heated for the stated time with microwaves. The resin was washed with ethanol (3 x 10 mL) and THF (3 x 10 mL), and then dried.

The yield of **8** was estimated from ELSD by evaporating the filtrate from the resin wash, dissolving the residue in methanol (4 mL), diluting a sample (0.1 mL) to 1 mL and analyzing.

Attempted optimization of nucleophilic cleavage of 7 (Cont.)

| Entry | Base /equiv | Solvent | conditions | IR (cm ⁻¹) | Yield 8 | Carbamate content by ELSD |
|-------|----------------------------------------------------------------------------------------|---------------------------|---------------|------------------------|----------------|---------------------------|
| 1 | KOH/ 1.5 equiv | ethanol/ 6% water | 150°C, 30 min | 1702 | 16 % | 29 % |
| 2 | LiOH/ 1.5 equiv | ethanol/ 6% water | 150°C, 30 min | 1701 | 16 % | 25 % |
| 3 | NaOH/ 1.5 equiv | ethanol/ 6% water | 150°C, 30 min | 1701 | 16 % | 27 % |
| 4 | LiOH/ 1.5 equiv | methanol/ 6% water | 150°C, 30 min | 1702 | 41 % | none |
| 5 | LiOH/ 1.5 equiv | methanol/ 53% water | 150°C, 30 min | 1701 | 15 % | none |
| 6 | LiOH/ 1.5 equiv | methanol/ 6% water | 150°C, 60 min | 1702 | 41 % | none |
| 7 | HBr/ 5 equiv | methanol/ water (5 %) | 150°C, 30 min | 1704 | none | none |
| 8 | KOH/ 5 equiv | methanol/ water (25%) | 150°C, 30 min | 1702 | 45% | none |
| 9 | LiOH*H ₂ O/ 5 equiv | methanol/ water (25 %) | 150°C, 30 min | 1701 | 45% | none |
| 10 | LiOH*H ₂ O/ 5 equiv | methanol/ water (25 %) | 150°C, 90 min | 1701 | 56 % | none |
| 11 | LiOH*H ₂ O/ 5 equiv AND H ₂ O ₂ / 5 equiv | methanol/ water (6 %) | 150°C, 30 min | 1701 | 45% | none |
| 12 | KOH/ 5 equiv | methanol | 150°C, 60 min | no peak | 55% | none |
| 13 | LiOH*H ₂ O/ 10 equiv | methanol | 150°C, 60 min | 1701 | 52% | none |

7.3.1.4 Optimization of addition and reductive cleavage

Comparison of phosgene and triphosgene as substrates for the formation of carbamate linker in the synthesis of 1-diphenylmethyl-4-methylpiperazine (**9**)

With Phosgene:

Versabeads O400 (3.0 g, 4.5 mmol, 1 equiv) was suspended in THF (30 mL) at room temperature. After 1 h a solution of phosgene in toluene (20 % w/w, 12 mL ($\rho = 0.935$ g/mL), 2.2 g, 22 mmol, 5 equiv) was added and the solution was stirred for 7 h. The suspension was filtered and the resin was washed successively with THF (3 x 30 mL), water (3 x 30 mL), methanol (3 x 30 mL), THF (3 x 30 mL), water (3 x 30 mL), and methanol (3x30 mL), then dried, to give resin (**4**). White beads.

IR = 1777 cm^{-1}

Elemental analysis: Cl – 4.3% ~ 1.21 mmol Cl/g ~ 88% loading

Resin **4** was suspended in a solution of 1-diphenylmethylpiperazine (5.67 g, 22.5 mmol, 5 equiv) in THF (60 mL) at room temperature. Triethylamine (3.1 mL ($\rho = 0.73$ g/mL), 2.3 g, 22.5 mmol, 5 equiv) was added and the suspension was stirred overnight. The resin was filtered, washed with THF (3 x 30 mL), water (3 x 30 mL), methanol (3 x 30 mL), THF (3 x 30 mL), water (3 x 30 mL) and methanol (3 x 30 mL), then suspended in THF (40 mL). Methanol (1.8 mL ($\rho = 0.79$ g/mL), 1.4 g, 45 mmol, 10 equiv) was added, followed by solid LiBH_4 (0.98 g, 45 mmol, 10 equiv). The suspension was heated to reflux and kept at reflux overnight. The reaction was quenched through slow addition of acetone (40 mL). The suspension was filtered and the resin was washed with 1 M aqueous HCl (2 x 200 mL), diethyl ether (50 mL), 1M aqueous KOH (50 mL) and diethyl ether (2 x 150 mL), then dried. IR of resin showed no CO stretch at 1701 cm^{-1}

The organic phase was separated from the filtrate and the aqueous phase was made basic with aqueous NH_3 (20 mL, 25 % v/w) and extracted with diethyl ether (50 mL, then 2 x 150 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (2 x 100 mL), brine (2 x 100 mL) and water (2 x 100 mL), dried (anhyd sodium sulphate) and evaporated.

End weight 1.02 g of a mixture of **8** and **9**.

^1H NMR (500 MHz, CDCl_3): $\delta = 2.20$ (s, 3 H, H1, **9**); 2.24-2.50 (m, 4H, H2, **8** and **9**); 2.84 (m, 4H, H3, **8** and **9**); 4.14 (s, H4, **9**); 4.15 (s, H4, **8**), 7.06-7.11 (m, H5, **8** and **9**); 7.16-7.21 (m, H6, **8** and **9**); 7.30-7.36 (m, H7, **8** and **9**).

Distribution by ^1H NMR (4.14/4.15 peak comparison): 62 mol % **9**.

With triphosgene/pyridine:

Versabeads O400 (3.0 g, 4.5 mmol, 1 equiv) was suspended in THF (30 mL) at room temperature. After 45 min triphosgene (2.2 g, 7.5 mmol, 5 equiv) was added and the suspension was cooled on ice/water bath. After 15 min py (1.7 mL ($\rho = 0.978$ g/mL), 1.66 g, 21 mmol, 5 equiv) was added, the cooling bath was removed and the suspension was stirred for 7 h. The suspension was filtered, and the resin was washed successively with THF (3 x 30 mL), water (3 x 30 mL), methanol (3 x 30 mL), THF (3 x 30 mL), water (3 x 30 mL) and methanol (3 x 30 mL) and then dried to give resin **4**. Reddish beads. (IR = 1777 cm^{-1} ; 1745 cm^{-1})

Elemental analysis: Cl – 3.8% ~ 1.08 mmol Cl/g ~ 79% loading.)

The resulting resin **4** was suspended in a solution of 1-diphenylmethylpiperazine (**8**) (5.67 g, 22.5 mmol, 5 equiv) in THF (60 mL) at room temperature. Triethylamine (3.1 mL ($\rho = 0.73$ g/mL), 2.3 g, 22.5 mmol, 5 equiv) was added and the suspension was stirred overnight. The suspension was filtered, and the resin was washed with THF (3 x 30 mL), water (3 x 30 mL), methanol (3 x 30 mL), THF (3 x 30 mL), water (3 x 30 mL) and methanol (3 x 30 mL), then suspended in THF (40 mL). Methanol (1.8 mL ($\rho = 0.79$ g/mL), 1.4 g, 45 mmol, 10 equiv) was added, followed by solid LiBH₄ (0.98 g, 45 mmol, 10 equiv). The suspension was kept at reflux overnight. The reaction was quenched through slow addition of acetone (40 mL) (CAREFUL! Exothermic!). The resin was filtered and washed with 1M aqueous HCl (2 x 200 mL), diethyl ether (50 mL), 1 M aqueous KOH (50 mL), diethyl ether (2 x 150 mL), then dried. IR of resin showed no CO stretch at 1701 cm⁻¹

The organic phase was separated from the filtrate and the aqueous phase was made basic with aqueous NH₃ (20 mL, 25 % v/w) and extracted with diethyl ether (50 mL, 2 x 150 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (2 x 100 mL), brine (2 x 100 mL) and water (2 x 100 mL), dried (anhyd sodium sulphate) and evaporated.

End weight 0.63 g of a mixture of **8** and **9**.

¹H NMR (500 MHz, CDCl₃): δ = 2.28 (s, 3H, H1, **9**); 2.24-2.74 (m, H2, **8** and **9**); 2.90 (dd, H3, **8** and **9**); 4.21 (s, 1H, H4, **9**) 4.22 (s, 1H, H4, **8**); 7.14-7.19 (m, 2H, H5, **8** and **9**); 7.23-7.28 (m, 4H, **8** and **9**, H6); 7.38-7.43 (m, 4H, H7, **8** and **9**).

Percent **9** (by NMR): 44 mol%

Identification of the impurities from reductive cleavage (10** and **11**²⁰⁵) through treatment of Versabeads with lithium borohydride.**

Versabeads VO400 (12.2 g, 23.3 mmol, 1 equiv) were suspended in THF (300 mL). Methanol (9 mL ($\rho = 0.79$ g/mL), 7.1 g, 220 mmol, 10 equiv) was added and the suspension was cooled on an ice/wate bath. Lithium borohydride (5.0 g, 230 mmol, 10 equiv) was added and the suspension was heated at reflux for 21 h.

The reaction was quenched with acetone (40 mL) and the suspension was filtered. The resin was washed with THF (3 x 100 mL) and 1 M aqueous HCl (3 x 100 mL). The filtrate was made basic with aqueous ammonia (25 % w/v, 100 mL) and extracted with diethyl ether (1 x 200 mL and 2 x 100 mL). The combined organic phases are washed with saturated aqueous sodium bicarbonate (2 x 50 mL), brine (2 x 50 mL) and water (2 x 50 mL), dried (anhyd sodium sulphate) and evaporated)

End weight 400 mg

Resin end weight 12.1 g (Difference 0.3 g)

¹H NMR (500 MHz, CDCl₃): δ = 1.10 (3H, d, **11**, H1); 1.15 (3H, s, **11**, H2); 1.21 (3H, s, **11**, H3); 1.35 (9H, s, **10**, H1); 1.38 (1H, dd, $J_1 = 2$ Hz; $J_2 = 14.5$ Hz, **11**, H4); 1.56 (1H, dd, $J_1 = 10.9$ Hz, $J_2 = 14.3$ Hz, **11**, H5); 2.18 (3H, s, **10**, H2); 4.11 (1H, d sextet, $J = 2.3$ Hz, **11**, H6); 4.30-4.06 (m, 2H, **11**, -OH); 4.97 (1H, s, **10**, H3); 6.89 (2H, s, **10**, H4).

Comparison of reductive cleavage of 7 with lithium borohydride and lithium aluminium hydride:

With lithium borohydride:

Resin 7 (5.3 g, 6.3 mmol, 1 equiv) was suspended in THF (80 mL) with methanol (2.4 mL ($\rho = 0.75$ g/mL), 1.8 g, 58 mmol, 9 equiv) and lithium borohydride (1.4 g, 64 mmol, 10 equiv) and heated to reflux. The reaction was kept at reflux overnight, then quenched with acetone (10 mL) and filtered. The resin was washed with THF (2 x 100 mL), 2 M aqueous HCl (2 x 100 mL) and THF (100 mL), then made basic with aqueous ammonia (25 % w/v, 100 mL) and extracted with diethyl ether (3 x 100 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (2 x 50 mL), brine (2 x 50 mL) and water (2 x 50 mL), dried (anhydrous sodium sulphate) and evaporated.

Yield: 1.0 g

^1H NMR (500 MHz, CDCl_3): 50:50 mixture of **8** and **9** judged by the peaks at 4.2 ppm.

^{13}C gel phase NMR of resin after cleavage shows very small aromatic peaks at $\delta = 127.5$ and 126.8.

With lithium aluminium hydride

Resin 7 (5.0 g, 6.2 mmol, 1 equiv) was suspended in THF (80 mL). Lithium aluminium hydride (2.4 g, 63 mmol, 10 equiv) was added and the suspension was heated at reflux temperature overnight. The reaction was quenched by the addition of water (2.5 mL), aqueous sodium hydroxide (28 %, 2.5 mL) and water (7 mL). The suspension was filtered and then the resin was washed with THF (2 x 100 mL) and 2 M aqueous hydrochloric acid (3 x 75 mL). An organic phase was separated from the filtrate and the aqueous phase was made basic with aqueous ammonia (25 % w/v, 100 mL), and extracted with diethyl ether (3 x 100 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (2 x 50 mL), brine (2 x 50 mL) and water (2 x 50 mL), dried (anhydrous sodium sulphate) and evaporated.

Yield 0.6 g of crude **9** (NO compound **8** by NMR) (36%)

^1H NMR (500 MHz, CDCl_3): $\delta = 1.42$ (water); 2.26 (s, 3 H, H1); 2.28-2.58 (m, 8 H, H2/H3); 4.21 (s, 1H, H4); 7.15 (m, 2H, H5); 7.25 (m, 4H, H6); 7.41 (m, 4H, H7)

^{13}C gel-phase NMR (62.5 MHz, CDCl_3) of resin showed incomplete cleavage of **7** (Peaks from aromatic at $\delta = 142.1$, 128.5, 127.8 and 127.3, and aliphatic at 51.5).

Optimization of the synthesis of resin 4 with phosgene (Table 6)

Versabeads O400 (1 g, 1.91 mmol, 1 equiv) were suspended in THF (11 mL). A solution of phosgene in toluene (20% w/w, amounts as stated in table 6) was added and the stirred for the time. The resins were filtered, washed with THF (2 x 10 mL), methanol (2 x 10 mL), THF (10 mL), then dried. Cl - analysis results as stated in table 6.

7.3.1.5 Attempted nucleophilic cleavage of carbamate linker

Synthesis of resin 12 from 1-(3,4-dichloropiperazine)

Versabeads O400 (5.4 g, 10.3 mmol, 1 equiv) were suspended in THF (70 mL). A solution of phosgene in toluene (20 w/w, 12 mL ($\rho = 0.935$ g/mL), 2.2 g phosgene, 23 mmol, 2.2 equiv) was added and the suspension was stirred for 2 h. Solvent was removed and the resin was washed with THF (2 x 70 mL) and methanol (2 x 70 mL). 1-(3,4 – dichlorophenyl)-piperazine (6 g, 26 mmol, 2.5 equiv) and triethylamine (7.1 mL ($\rho = 0.73$ g/mL), 9.7 g, 96 mmol, 9 equiv) was added as a solution in THF (50 mL) and the suspension was agitated overnight. The suspension was sucked dry and the resin was washed with THF (2 x 70 mL), methanol (2 x 70 mL), water (2 x 70 mL) and THF (2 x 70 mL) then dried, to give resin **12**

^{13}C gel-phase NMR (62.5 MHz, CDCl_3): 154.9 (C1); 150.3 (C2); 132.6 (C3); 130.3 (C4); 122.6 (C5); 117.6 (C6); 72.3 ($-\underline{\text{CH}}_2\text{CH}_2\text{OH}$); 70.3 (framework) 69.3 ($-\underline{\text{CH}}_2\text{CH}_2\text{OR}$); 64.5 ($-\text{CH}_2\underline{\text{CH}}_2\text{OR}$); 61.4 ($-\text{CH}_2\underline{\text{CH}}_2\text{OH}$); 48.5 (C7); 43.2 (C8); 40.9, 23.0, 17.3, 7.5 (framework).

Conversion judged by peaks at 64 and 61 ppm: 50 %

Attempted cleavage of resin 12 with aqueous base

Resin **12** was suspended in water (20 mL). KOH (0.73 g, 12.5 mmol, 5 equiv) was added. The suspension was heated to reflux and kept at this temperature for 6 h. The suspension was filtered and the resin was washed with THF (2 x 20 mL), 1 M aqueous HCl (2 x 70 mL) and THF (2 x 70 mL) and then dried.

^{13}C gel-phase NMR (62.5 MHz, CDCl_3) showed no change from resin **12**.

Attempted synthesis of 1-(3,4-dichlorophenyl)-piperazine 1-decyl carbamate 13.

Resin **12** (2 g, ca. 1.3 mmol, 1 equiv) was suspended in DME (20 mL). 1-decanol (1.0 g, 6.9 mmol, 5 equiv) and potassium *tert*-butoxide (0.72 g, 6.4 mmol, 5 equiv) was added and the suspension was heated to reflux and kept at this temperature for 2 h. The suspension was filtered and the resin was washed with DME (3 x 20 mL), 1 M aqueous HCl (3 x 20 mL), DME (1 x 20 mL) and 1 M aqueous HCl (3 x 20 mL) and then dried. DME was evaporated from filtrate and the aqueous phase was washed with ethyl acetate (2 x 50 mL) then made basic with aqueous ammonia (25 % w/v, 100 mL). The aqueous phase was extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (30 mL), brine (30 mL) and water (2 x 30 mL) and dried (anhydrous sodium sulphate) and evaporated) to yield only free 1-(3,4 dichlorophenyl)piperazine and 1 –decanol by NMR.

7.3.2 REM linker synthesis

7.3.2.1 Attempted synthesis of sulphone REM linker 14 based on Hoffmann addition of divinyl sulphone (Table 7).

With DBU (table 7, entry 1)

Versabeads O400 (1 g, 0.5 mmol, 1 equiv) was suspended in dichloromethane (12 mL) with DBU (75 μ L (ρ = 1.018 g/mL), 76 mg, 0.5 mmol, 1 equiv) at room temperature. Divinyl sulphone (0.6 mL (ρ = 1.177 g/mL), 0.71 g, 6 mmol, 12 equiv) was added slowly and the suspension was left at room temperature overnight. The resin was filtered, washed with dichloromethane (3 x 5 mL) and methanol (6 x 5 mL), then dried.

^1H MAS NMR: Small peaks between 6 and 7 ppm.

IR showed no vinylic stretch (2000-1500 cm^{-1})

Elemental analysis for S: calc: 1.5% (w/w) found 0.6 % (w/w)

^{13}C -NMR: no change

A sample of the resin (0.5 g) was suspended in dry DMF (7.5 mL). *N*-benzyl-*N*-methylamine (0.1 mL (ρ = 0.94 g/mL), 94 mg, 0.78 mmol) was added and the suspension was shaken overnight. The suspension was filtered and the resin was washed with dichloromethane (3 x 5 mL) and dried.

^1H MAS NMR showed no change after the reaction.

With Triton B (table 7, entry 2)

Versabeads O400 (2.02 g, 1 mmol, 1 equiv) was suspended in dichloromethane (50 mL) with divinyl sulfone (0.15 mL (ρ = 1.177 g/mL) 0.18 g, 1.5 mmol, 1.5 equiv) at room temperature. After 1 h 3 drops of Triton B (a 40 % aqueous solution of *N*-benzyl-*N*-trimethylammonium hydroxide) was added and the reaction was left for 4 days. The resin was filtered, washed with toluene (6 x 20 mL) and dichloromethane (6 x 20 mL) and then dried.

IR did not change.

^1H -MAS NMR (500 MHz; CD_2Cl_2) showed no vinylic protons (5-7 ppm).

Elemental analysis for S: calc: 1.5 % (w/w) found 0.7 % (w/w)

Resin (0.97 g, 0.5 mmol, 1 equiv) was suspended in DMF (3 mL) at room temperature. 1-benzyl piperazine (0.86 mL (ρ = 0.87 g/mL), 0.88 g, 5 mmol, 10 equiv) was added, and the suspension was left overnight. The suspension was filtered and the resin was washed with DMF (10 mL), THF (10 mL) and toluene (10 mL), then dried.

^{13}C gel phase NMR (CDCl_3 , 62.5 MHz) showed no aromatic protons and no vinylic protons. Peaks at 72.1 ppm ($-\underline{\text{C}}\text{H}_2\text{CH}_2\text{OH}$) and 61.0 ppm ($-\text{CH}_2\underline{\text{C}}\text{H}_2\text{OH}$) indicated unloaded resin.

With NaOH (table 7, entry 3)

Versabeads O400 (1.5 g, 0.75 mmol, 1 equiv) were suspended in THF (9 mL). After 1 h divinyl sulphone (0.69 mL ($\rho = 1.177$ g/mL), 0.81 g, 6.9 mmol, 9 equiv) was added followed by slow addition of 1 M aqueous sodium hydroxide (0.26 mL, 0.26 mmol, 0.35 equiv). The suspension was stirred for 3 days.

The resin was filtered, washed with alternating THF (20 mL) and water (20 mL) 6 times, then with dichloromethane (2 x 20 mL). Dried in vacuo at room temperature.

^1H MAS NMR (500 MHz, CD_2Cl_2) showed no vinylic peaks (6-7 ppm)

IR showed no vinylic stretch ($2000\text{-}1500\text{ cm}^{-1}$)

A sample of the resin (0.5 g) was suspended in DMF (2 mL). 1-benzyl piperazine (0.7 mL ($\rho = 0.87$ g/mL), 0.61 g, 3.5 mmol) was added and the suspension was allowed to stand overnight, then sucked dry

^1H MAS NMR (500 MHz, CD_2Cl_2) showed a new peak at 8.0 ppm (Probably DMF)

IR showed stretch at ca. 1700 cm^{-1} (DMF)

7.3.2.2 Attempted synthesis of resin 15 through metathesis with allyl-functionalized Versabeads.

With Grubbs catalyst:

Allylated Versabeads O400 (1.0 g, 0.5 mmol, 1 equiv) were thoroughly dried, then placed in a dry flask under N_2 , and suspended in dichloromethane (30 mL) dried over anhydrous calcium chloride. Divinyl sulphone (0.10 mL ($\rho = 1.177$ g/mL), 118 mg, 1 mmol, 2 equiv) was added and the suspension was degassed. Grubbs catalyst (43 mg, 0.05 mmol, 0.1 equiv) was added, and the suspension was kept at reflux overnight.

^1H MAS NMR: no vinyl sulfone protons visible (6-7 ppm)

IR stretch at 1720 cm^{-1} replaced by small stretch at 1630 cm^{-1}

Elemental analysis for S: calc: 1.1% (w/w) found 0.02 % (w/w)

With Hoveyda carbene catalyst:

Allylated Versabeads O400 (1.0 g, 0.5 mmol, 1 equiv) were thoroughly dried, then placed in a dry flask under N_2 and suspended in dichloromethane (40 mL) dried over anhyd calcium chloride. Divinyl sulfone (0.30 mL ($\rho = 1.177$ g/mL) 0.36 g, 3 mmol, 6 equiv) was added and the suspension was degassed. Hoveyda carbene catalyst (38 mg, 0.05 mmol, 0.1 equiv) was added, and the suspension was kept at reflux for 20 h, then filtered. the resin was washed with DCM (6 x 10 mL) and THF (6 x 10 mL) then dried.

IR and ^1H MAS NMR was identical to starting material. ^{13}C gel-phase NMR showed no carbons corresponding to those expected from metathesis (128-149 ppm).

7.3.2.3 Synthesis and test of acrylic acid based REM linker

Acrylic acid linker 16 – general procedure

Versabeads O400 (5.15 g, 5.6 mmol, 1 equiv) were suspended in dichloromethane (70 mL) at room temperature. DIPEA (10 mL ($\rho=0.75$ g/mL), 7.3 g, 56 mmol, 10 equiv) was added, followed by slow addition of acryloyl chloride (5.7 mL ($\rho=1.11$ g/mL), 5.2 g, 56 mmol, 10 equiv). The suspension was stirred overnight, then filtered, and the resin was washed with dichloromethane (3 x 50 mL) and THF (3 x 50 mL) and then dried to give 5.56 g (131% of theoretical weight gain) of resin **16**.

IR: 1724 cm^{-1} (CO stretch)

^{13}C gel phase NMR: (CD_2Cl_2 , 62.5 MHz): δ = 171.0 (resin impurity); 166.5 (C1); 131.5 (C2); 129.1 (C3); 74.4; 71.3 (framework); 69.8 ($\text{CH}_2\text{CH}_2\text{OR}$); 67.6 (framework); 64.5 ($\text{CH}_2\text{CH}_2\text{OR}$); 41.9, 41.0, 39.9, 21.6, 17.9 (framework).

Hoffmann Addition of 1 - diphenylmethyl piperazine to resin 16 to form resin 17.

Resin **15** (0.5 g, 0.25 mmol, 1 equiv) was suspended in dry DMF (3 mL) in a syringe. A solution of 1-dimethylphenylpiperazine (0.65 g, 2.6 mmol, 10 equiv) in DMF (3 mL) was added and the suspension was agitated at room temperature overnight. The suspension was filtered and the resin was washed with DMF (3 x 5 mL) and THF (3x5 mL), then with THF overnight (5 mL) then alternating THF and DCM for 3 cycles, then dried to yield 0.56 g (78% of theoretical weight gain) of resin **17**.

^{13}C gel phase NMR: (62.5 MHz, CDCl_3): 171.5 (C1); 142.0 (C2); 127.7 (C3); 127.2 (C4); 126.3 (C5); 69.9 (framework); 62.8 ($-\text{CH}_2\text{CH}_2\text{OR}$); 52.6 (C6/C7); 51.1 (C8); 42.7 (framework); 31.6 (C9); 22.4; 7.1 (framework)

^1H MAS NMR: 2.4; 2.6 (piperazine) 7.0 – 7.4 (aromatics)

IR= 1732 cm^{-1}

Alternative addition of 1-diphenylmethylpiperazine to 16, using THF as solvent.

Versabeads O400 (4.3 g, 4.7 mmol, 1 equiv) was suspended in dichloromethane (60 mL). DIPEA (8.5 mL ($\rho=0.73$ g/mL), 6.4 g, 50 mmol, 10 equiv) was added followed by slow addition of acryloyl chloride (5 mL ($\rho=1.11$ g/mL), 5.5 g, 61 mmol, 13 equiv). The suspension was stirred overnight at room temperature, then filtered, and the resin was washed with dichloromethane (3 x 60 mL), to give resin **16**

The resin was suspended in a solution of 1-diphenylmethylpiperazine (6.0 g, 24 mmol, 5 equiv) in THF (65 mL) and the suspension was stirred overnight at room temperature. The suspension was filtered, washed with THF (3 x 30 mL), methanol (3 x 30 mL), DCM (3 x 30 mL) and THF (3 x 30 mL) then dried.

^{13}C gel-phase NMR: (62.5 MHz, CD_2Cl_2): δ = 173.2 (C1); 171.0 (resin impurity); 144.0 (C2); 129.3 (C3); 128.6 (C4); 127.7 (C5); 77.0 (C6); 71.4 (framework); 64.4 ($-\text{CH}_2\text{CH}_2\text{OR}$); 52.7 (C7); 41.9 (framework); 33.1 (C8); 21.6, 18.0 (framework).

Solid phase synthesis of **19** on gram-scale from REM functionalized resin **16** with quaternization in water

Resin **16** (3.1 g, 3.8 mmol, 1 equiv), was suspended in a solution of 1-dimethylphenylpiperazine (4.6 g, 18.3 mmol, 4.8 equiv) in THF (120 mL) and the suspension was stirred overnight at room temperature. The suspension was filtered and the resin was washed with THF (3 x 30 mL), methanol (3 x 30 mL) and THF (3 x 30 mL) and then dried. The resin was suspended in water (20 mL). Allyl bromide (2.0 g, 16 mmol, 5 equiv) was added and the suspension was stirred at room temperature overnight. The suspension was filtered, and the resin was washed with water (3 x 30 mL), methanol (3 x 20 mL), THF (3 x 20 mL) and methanol (1 x 30 mL).

Analysis of the washing by LC/MS revealed the presence of significant amounts of compound **19**, cleaved off prematurely.

The resin was suspended in dichloromethane (20 mL). DIPEA (1.2 mL ($\rho = 0.73$ g/mL), 0.88 g, 6.7 mmol, 2 equiv) was added and the suspension was stirred for 8 h. The suspension was filtered and the resin was washed with alternating DCM (30 mL) and methanol (30 mL) three times and then dried.

IR CO stretch = 1725 cm^{-1} (= **16**)

The filtrate was evaporated and dissolved in diethyl ether (50 mL) and water (50 mL). The phases were separated and the water phase was extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with saturated aqueous sodium carbonate (20 mL), dried (anhydrous sodium sulphate) and evaporated to give compound **19** as off-white crystals.

Yield: 0.24 g (21 %)

^1H -NMR (CDCl_3 , 500 MHz): $\delta = 2.00 - 2.90$ (m, 8H, H1); 2.99 (d, $J = 6.7$ Hz, 2H, H2); 4.21 (s, 1H, H3); 5.11 (d, $J = 10.3$ Hz, 1H, H4); 5.16 (d, $J = 17.3$ Hz, 1H, H5); 5.85 (ddt, $J^1 = 17.1$ Hz, $J^2 = 10.4$ Hz, $J^3 = 6.4$ Hz, 1H, H6); 7.15 (dd, $J^1 = 7.4$ Hz, $J^2 = 7.4$ Hz, 2H, H7); 7.25 (dd, $J^1 = 7.4$ Hz, $J^2 = 7.4$ Hz, 4H, H8); 7.40 (d, 7.8 Hz, 4H, H9).

^{13}C NMR (62.5 MHz, CDCl_3): $\delta = 142.1$ (C1); 134.4 (C2); 127.8 (C3); 127.3 (C4); 126.2 (C5); 117.3 (C7); 75.6 (C8); 61.1 (C9); 52.7 (C10); 51.2 (C11).

Anal Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_2$: C, 82.14; H, 8.27; N, 9.58. Found: C, 82.05; H, 8.16; N, 9.50.

7.3.2.4 Microwave assisted synthesis of **19** from resin **16**

Versabeads O400 (3.4 g, 5.5 mmol, 1 equiv) were suspended in dichloromethane (50 mL). DIPEA (2.8 mL ($\rho = 0.755$ g/mL), 2.1 g, 16 mmol, 3 equiv) was added at room temperature, followed by a slow addition of acryloyl chloride (4.45 mL ($\rho = 0.755$ g/mL) 5 g, 55 mmol, 10 equiv) in dichloromethane (15 mL). The suspension was stirred for 19 h, then filtered, washed with DCM (3 x 30 mL), acetonitrile (1x 30 mL) DCM (1x 30 mL) then dried. End weight 3.9 g (88% of theoretical weight gain.)

^{13}C - gel phase NMR (62.5 MHz, CD_2Cl_2): 170.0 (C1); 131.5 (C2); 129.2 (C3); 71.3 (framework); 69.8 ($\text{CH}_2\text{CH}_2\text{OR}$); 64.5 ($\text{CH}_2\text{CH}_2\text{OR}$); 44.2, 24.0, 8.3 (framework).
IR (Carbonyl): 1724 cm^{-1}

Resin (1.2 g, 1.3 mmol, 1 equiv) was suspended in a solution of 1 - diphenylmethylpiperazine (1.63 g, 6.5 mmol, 5 equiv) in THF (4 mL) in an Emrys Process Vial (5 mL) and heated with microwaves (60 °C, 1 h), The resin was filtered and washed with THF (1 x 5 mL), methanol (1 x 5 mL), water (1 x 5 mL), THF (1 x 5 mL), DMF (1 x 5 mL), dichloromethane (1 x 5 mL), water (1 x 5 mL) and THF (1x5 mL), to give resin **17**

The resin **17** was suspended in water (4 mL) with allyl bromide (0.54 mL ($\rho = 1.43$ g/mL), 0.77 g, 6.4 mmol, 5 equiv) in an Emrys Process Vial (5 mL), the vial was sealed and the suspension heated with microwaves (60°C, 1 h). The suspension was filtered and the resin was washed with THF (1 x 5 mL), DMF (1 x 5 mL), THF (1 x 5 mL), Methanol (1 x 5 mL) THF (1 x 5 mL), DCM (2x 5 mL) and THF (2 x 5 mL).

The resin was suspended in dichloromethane (5 mL) in an Emrys Process Vial (5 mL). DIPEA (0.45 mL ($\rho = 0.77$ g/mL), 0.35 g, 2.8 mmol, 2.2 equiv) was added, the vial was sealed and the suspension was heated with microwaves (60 °C, 45 min). The suspension was filtered and the resin was washed with DCM (3 x 5 mL) and methanol (3 x 5 mL). The filtrate was evaporated to give 153 mg (40%) of **19**.

^1H NMR (500 MHz, CDCl_3): 2.47 (br s, 8H, H1); 3.00 (d, 2H, $J = 6.6$ Hz, H2) 4.22 (s, 2H, H3) 5.10 – 5.13 (m, 1H, H4); 5.14-5.19 (m, 1H, H5); 5.85 (ddt, $J^1 = 17.3$ Hz, $J^2 = 10.6$ Hz, $J^3 = 6.2$ Hz, 1H, H6); 7.14-7.19 (m, 2 H, H7); 7.22 – 7.28 (m, 4H, H8); 7.39 – 7.43 (m, 4H, H9)

^{13}C NMR (62.5 MHz, CDCl_3): $\delta = 142.8$ (C1); 135.0 (C2); 128.4 (C3); 127.9 (C4); 126.9 (C5); 118.0 (C7); 76.2 (C8); 61.7 (C9); 53.3 (C10); 51.8 (C11).

CHN calc for $\text{C}_{20}\text{H}_{24}\text{N}_2$: C, 82.14 H, 8.27; N, 9.58 Found: C, 81.81 H, 8.04 N, 9.56

7.3.2.5 Addition of piperazine to resin 16 and subsequent derivatization

Hofmann addition of piperazine to REM-functionalized resin 16 to form resin 20.

Resin **16** (4.65 g, 3.9 mmol, 1 equiv) was suspended in a solution of piperazine (4 g, 46 mmol, 12 equiv) in DMF (90 mL) at room temperature and the suspension was stirred overnight. The suspension was filtered and the resin was washed with DMF (3 x 40 mL), methanol (3 x 40 mL), THF (3 x 40 mL) and DCM (3 x 40 mL) and then dried.

End weight: 4.85 g (59% of theoretical weight gain) of resin **20**.

^{13}C gel phase NMR: (CD_2Cl_2 , 62.5 MHz): δ = 171.0 (resin impurity); 71.5 (framework); 64.5 ($\text{CH}_2\text{CH}_2\text{OR}$); 61.8 ($\text{CH}_2\text{CH}_2\text{OH}$); 46.8 (C1); 41.9 (framework); 33.1 (C2); 21.5, 18.0 (framework).

IR: 1734 cm^{-1} (CO stretch); 1641 cm^{-1} (possibly DMF)

Synthesis of 1-allyl-4-phenylaminocarbonyl (22)

Resin **20** (1.52 g, 1.17 mmol, 1 equiv) was suspended in DMF (20 mL). Phenyl isocyanate (1.26 mL ($\rho=1.096$ g/mL), 1.39 g, 11.7 mmol, 10 equiv) was added and the solution was agitated in a syringe at room temperature overnight. The suspension was filtered, washed with DMF (3 x 20 mL), THF (3 x 20 mL), methanol (3 x 20 mL) and THF (3 x 20 mL) and then dried

End weight 1.61 g of resin **21** (65% of theoretical weight gain)

^{13}C gel phase NMR: (CD_2Cl_2 , 62.5 MHz): δ = 172.8 (C1); 171.0 (resin impurity); 156.1 (C2); 141.1 (C3); 129.5 (C4); 123.0 (C5); 120.9 (C6); 71.4 (framework); 67.6 (framework); 64.4 ($\text{CH}_2\text{CH}_2\text{OR}$); 44.8 (C7) 42.0, 40.0 (framework); 33.1 (C8) 21.6, 17.9 (framework).

Resin **21** (1.22 g, 0.76 mmol, 1 equiv) was suspended in water (10 mL) in a syringe. Allyl bromide (0.361 mL ($\rho=1.43$ g/mL), 0.51 g, 4.2 mmol, 5.5 equiv) was added and the suspension was agitated overnight at room temperature. The suspension was filtered, and the resin was washed with THF (3 x 10 mL), methanol (3 x 10 mL) and THF (3 x 10 mL) and then dried. The resin was suspended in dichloromethane (7.5 mL) at room temperature. DIPEA (0.42 mL ($\rho=1.096$ g/mL), 0.31 g, 2.3 mmol, 3 equiv) was added and the suspension was stirred for 7 h under N_2 , then filtered. The resin was washed with THF (3 x 10 mL) and DCM (3 x 10 mL) and then dried.

^{13}C gel phase NMR (62.5 MHz, CD_2Cl_2) shows remaining compound on resin, but very little cleavage of the REM linker from resin (small peak at 62 ppm compared to 64 ppm)

IR of resin: 1726 cm^{-1} (= **16**);

Filtrate from cleavage was evaporated. The residue was dissolved in a solution of ammonium chloride (1.7 g in 16 mL) which was acidified to pH = 0 with HCl (conc.), then basified with NaOH to pH=14 and extracted with ethyl acetate (6 x 20 mL). The

combined organic phases were washed with saturated aqueous sodium carbonate (2 x 20 mL) then dried (anhyd sodium sulphate) and evaporated to give 100 mg of crude **22** (35%) (UV purity = 83%)

¹H-NMR (CDCl₃, 500 MHz): δ = 0.9-1.3 (impurities); 1.43 (water); 2.38-2.44 (4H, m, H1); 2.99 (2H, d, J = 6.6 Hz, H2); 3.44-3.50 (4H, m, H3); 5.17 (1H, d, J = 9 Hz, H4); 5.20 (1H, d, J = 15.5 Hz, H5); 5.84 (1H, ddt, J₁ = 16.3 Hz, J₂ = 10.3 Hz, J₃ = 6 Hz, H6); 6.79-6.88 (1H, m, H7); 6.97-7.03 (1H, m, H8); 7.21-7.26 (2H, m, H9); 7.34 (2H, d, H10).

¹³C-NMR (CDCl₃, 100 MHz) 155.6 (C1); 139.6 (C2); 134.9 (C3); 129.2 (C4); 125.9 (impurity) 123.4 (C5); 120.6 (C6); 118.8 (C7); 62.0 (C8); 53.1 (C9); 44.4 (C10); 30.7, 30.1 (impurity)

Synthesis of 1-allyl-4-benzoylpiperazine (**24**)

Resin **20** (1.22 g, 0.94 mmol, 1 equiv) was suspended in dichloromethane (10 mL) at room temperature. Triethylamine (0.26 mL (ρ = 0.73 g/mL), 0.19 g, 1.9 mmol, 2 equiv) was added followed by dropwise addition of benzoyl chloride (0.22 mL (ρ = 1.211 g/mL), 0.27 g, 1.9 mmol, 2 equiv). The resulting suspension was stirred overnight at room temperature. Resin was filtered, washed with DCM (3 x 10 mL), THF (3 x 10 mL), methanol (3 x 10 mL) and THF (3 x 10 mL) and then dried to give 1.30 g (82% of the theoretical weight gain) of resin **23**.

¹³C gel phase NMR (62.5 MHz, CD₂Cl₂): 172.6 (C1); 171.0 (C2); 137.0 ppm (C3); 130.2 ppm (C4); 129.2 (C5); 127.8 (C6); 71.4 ppm, 67.9 ppm (framework) 64.4 (-CH₂-CH₂OR) 48.3 (C7) 33.1 (C8) 21.5 18.0 (framework)

Resin **23** (1.11 g; max. 0.79 mmol 1 equiv) was suspended in water (5 mL) with allyl bromide (0.33 mL, (ρ = 1.43 g/mL), 0.48 g, 3.9 mmol, 5 equiv) and stirred overnight at room temperature. Resin was filtered, washed with THF (3 x 10 mL), methanol (3 x 10 mL) and THF (3 x 10 mL), then dried. LC/MS of the washing solution reveals presence of prematurely cleaved product.

Resin was suspended in dichloromethane (7 mL) with stirring at room temperature. DIPEA (0.30 mL, (ρ = 0.73 g/mL) 0.41 g, 3.1 mmol, 4 equiv) was added and the suspension was stirred for 6 h. The resin was filtered and washed with DCM (10 mL) and methanol (10 mL) alternating 3 times. The filtrate was evaporated, and the residue was dissolved in a two-phase system of diethyl ether (40 mL) and saturated aqueous sodium carbonate (20 mL). The two phases were separated and the aqueous phase was washed with diethyl ether (2 x 20 mL). The combined organic phases were dried (anhyd sodium sulphate) filtered and evaporated to give 70 mg of crude compound **24** (38 %) (UV purity = 97%)

¹H-NMR (CDCl₃, 500 MHz): δ = 2.30-2.64 (m, 4H, H1), 3.03 (d, J = 6.9 Hz, 2H, H2); 3.36-3.88 (m, 4H, H3); 5.17 (dd, J₁ = 10.4 Hz, 1H, H4); 5.20 (dd, J₁ = 17.7 Hz, 1H, H5); 5.85 (ddt, J₁ = 6.7 Hz, J₂ = 6.6 Hz, J₃ = 13.5 Hz, H6); 7.40 (5H, m, H7)

^{13}C -NMR (CDCl_3 , 100 MHz): 170.7 (C1); 136.2 (C2); 134.8 (C3); 130.0 (C4); 128.8 (C5); 127.4 (C6); 118.9 (C7); 62.0 (C8); 53.7 (C9); 53.1 (C10); 48.1 (C11); 42.5 (C12).

7.3.3 Wang linker synthesis

Synthesis of Br functionalized Versabeads (**25**)

Versabeads O 400 (2.1 g, 2.3 mmol, 1 equiv) was suspended in dichloromethane (23 mL). Triphenylphosphine (2.8 g, 11 mmol, 4.8 equiv) and imidazole (0.84 g, 12 mmol, 5.4 equiv) was added and the suspension was cooled on an ice bath. Bromine (0.55 mL ($\rho=3.119\text{ g/mL}$), 1.7 g, 11 mmol, 4.8 equiv) was added slowly and the reaction was allowed to warm to room temperature. After 21 h the suspension was filtered and the resin was washed with DMF (2 x 20 mL), water (2 x 20 mL), 10% aqueous sodium thiosulfate (2 x 20 mL), water (2 x 20 mL), DMF (2 x 20 mL), dichloromethane (2 x 20 mL), then dried to give 2.4 g ~ (200 % of theoretical weight gain) of resin **25**.

^{13}C gel-phase NMR (62.5 MHz; CD_2Cl_2): δ =171.0 (resin impurity); 71.3 (framework); 68.5 ($-\text{CH}_2\text{CH}_2\text{Br}$); 43.9 (possibly oxethane formed?); 41.8 (framework); 26.3 ($-\text{CH}_2\text{CH}_2\text{Br}$); 21.6, 18.2 (framework)
Br elemental analysis: 2.75%; 2.57% 0.34 mmol Br/g (33% of theoretical loading)

Resin **25** (1.2 g, 1.2 mmol, 1 equiv) was suspended in a solution of 4-hydroxybenzylalcohol (0.46 g, 3.3 mmol, 2.8 equiv) and potassium iodide (5.3 mg, 32 μmol , 0.03 equiv) in DMF (8 mL). Potassium carbonate (0.53 g, 3.8 mmol, 3.2 equiv) was added and the suspension immediately grew dark. The suspension was heated to 60 ° C for 20 h, then filtered. The beads were very dark, mixed with crystals and seemed to have broken down to a significant degree. The resin was washed with DMF (3 x 10 mL), water (3 x 10 mL), *N*-methylpyrrolidone (3 x 10 mL), methanol (3 x 10 mL) and dichloromethane (2 x 10 mL), then suspended in water for 3 days. The resin was washed with 0.1 M aqueous HCl (3 x 10 mL), water (3 x 10 mL), methanol (3 x 10 mL) and THF (6 x 10 mL).

^{13}C gel-phase NMR (62.5 MHz, CDCl_3): δ = 169.7 (resin impurity); 70.0 (framework); 42.1 (oxethane); 40.4, 20.4, 17.0 (framework).

Synthesis of Wang linker **27** by Mitsunobu reaction and reduction.

Versabeads O 400 (1.4 g, 1.5 mmol, 1 equiv) was suspended in distilled THF (15 mL) at room temperature. Triphenylphosphine (0.86 g, 3.3 mmol, 2.2 equiv) and 4-hydroxybenzaldehyde (0.40 g, 3.3 mmol, 2.2 equiv) were added as a solution in distilled THF (10 mL). Diethyl azodicarboxylate (0.58 g, 3.3 mmol, 2.2 equiv) was added slowly as a solution in distilled THF (3 mL). The suspension was stirred at room temperature for 22 h, then filtered and the resin was washed with THF (3 x 20 mL), methanol (3 x 20 mL), THF (3 x 20 mL) and DCM (3 x 20 mL), then dried to give 1.46 g of resin **26** (33 % of theoretical yield). Beads strongly red.

^{13}C gel phase NMR (62.5 MHz, CD_2Cl_2): δ = 191.2 (C1); 171.0 (resin impurity); 132.8 (C2); 129.9 (C3); 116.9 (C4); 115.7 (C5); 71.4 (framework); 68.7 (- $\text{CH}_2\text{CH}_2\text{OR}$); 62.3 (- $\text{CH}_2\text{CH}_2\text{OH}$); 41.8 (framework); 39.9 (possible oxethane closure); 21.6, 18.1 (framework); 15.0 (possible oxethane closure)
IR: 1735 cm^{-1} ; 1689 cm^{-1} ; 1601 cm^{-1} ; 1578 cm^{-1} (similar to 4-methoxybenzaldehyde (Aldrich))

Resin **26** (1.23 g, 1.18 mmol, 1 equiv) was suspended in THF (12 mL) at room temperature. Sodium borohydride (0.21 g, 5.5 mmol, 4.7 equiv) was added as a suspension in *N*-methylmorpholine (7.8 mL) and ethanol (7.8 mL). The suspension was stirred overnight and then quenched through addition of water (10 mL). The suspension was filtered and the resin was washed with THF (3 x 20 mL), methanol (3 x 20 mL) and DCM (3 x 20 mL) and then dried to form resin **27**.

^{13}C gel phase NMR (62.5 MHz, CD_2Cl_2): δ = 159.0 (C1), 135.0 (C2) 129.0 (C3) 115.2 (C4) 71.3 (framework) 68.3 (- $\text{CH}_2\text{CH}_2\text{OR}$) 64.9 (C5) 41.7, 18.1 (framework)
 ^1H MAS NMR (CD_2Cl_2): 6.9, 6.7 (aromatics) 4.1 (- $\text{OC}_6\text{H}_4\text{CH}_2\text{OH}$)
IR showed no peaks between 1800-1500 cm^{-1} (aldehyde)

Synthesis of resin bound 4-hydroxybenzaldehyde **24** by nucleophilic addition to mesyl-functionalized Versabeads

Versabeads VO 400 (0.5 g, 0.75 mmol, 1 equiv) was suspended in freshly distilled dichloromethane (4 mL) at room temperature under Ar. Mesyl chloride (1.1 mL (ρ =1.48 g/mL), 1.7 g, 15 mmol, 20 equiv) was added and the suspension was cooled on an ice bath. Pyridine (0.5 mL (ρ =0.978 g/mL), 0.5 g, 6.2 mmol, 8 equiv) was added and the suspension was stirred for 1.5 h. The suspension was filtered and the reaction was repeated for 1 h, then the suspension was filtered, washed with DCM (3 x 5 mL), MeCN (3 x 5 mL) and DCM (1 x 5 mL) then dried to give resin **28**.

IR = 1174 cm^{-1} (SO)

4-hydroxybenzaldehyde (0.52 g, 4.3 mmol, 5.7 equiv) and sodium hydroxide (0.16 g, 4.0 mmol, 5.3 equiv) was suspended in DMF (10 mL) and heated to 90°C. After 30 min. the mesylated resin was added, and the suspension was stirred at 90 °C overnight. The suspension was filtered and the resin was washed with DMF (3 x 5 mL) and DCM (3 x 5 mL) and dried.

New IR peaks showed the characteristic peaks for **26**.

7.4 Synthesis of aryl piperazines from resin-bound mustards

7.4.1 Immobilization of the mustard

7.4.1.1 Initial synthesis (Table 11)

Initial synthesis of resin **29** in dichloromethane

Versabeads O400 (0.8 g, 0.4 mmol, 1 equiv) was suspended in THF (4 mL). A solution of phosgene in toluene (20% w/w, 2.5 mL, (ρ = 0.935 g/mL), 0.46 g phosgene, 4.7 mmol, 12 equiv) was added and the suspension was agitated overnight. The resin was washed with dry THF (4 mL), then suspended in a solution of bis(bromoethyl)amine, hydrobromide (0.60 g, 1.9 mmol, 5 equiv) and triethylamine (0.78 mL (ρ = 0.73 g/mL) 0.58 g, 5.7 mmol, 15 equiv) in dry dichloromethane (8 mL). The suspension was agitated for 24 h. The suspension was filtered and the resin was washed with dichloromethane (4 x 10 mL), THF (6 x 10 mL) and methanol (2 x 10 mL) and then dried to give resin **29** (weight not recorded)

^{13}C - gel phase NMR (62.5 MHz, CDCl_3): 154.8 (C1) 73.0, 69.9 (framework) 65.8 (morpholin, **30**) 64.1 ($-\text{CH}_2\text{CH}_2\text{OR}$) 49.8 (C2) 43.3 (morpholin, **30**) 40.6 (framework) 28.9 (C3) 16.7 (framework), 13.4 (possible ring closure artefact)
IR = 1702 cm^{-1} (Carbonyl stretch)

Estimated yield by ^{13}C gel phase NMR ~ 100 % (No ($-\text{CH}_2\text{CH}_2\text{OH}$) peak (61 ppm))
Br-analysis 6.4%/6.5% ~ 0.4 mmol mustard/g. (80 %)

Synthesis of resin **29** in water (table 11, entry 2)

Versabeads O400 (5.7 g, 8.6 mmol, 1 equiv) was suspended in THF (70 mL). A solution of phosgene in toluene (20% w/w, 22 mL, (ρ = 0.935 g/mL) 4.1 g phosgene, 41 mmol, 5 equiv) was added and the suspension was stirred at room temperature for 6 h. The suspension was filtered and the resin was washed with THF (3 x 50 mL) and methanol (3 x 50 mL). The resin was then suspended in a solution of bis(bromomethyl)amine, hydrobromide (13.3 g, 43 mmol, 5 equiv) in water (80 mL). Triethylamine (6 mL (ρ = 0.73 g/mL), 4.4 g, 43 mmol, 5 equiv) was added and the suspension was stirred overnight at room temperature. The suspension was filtered and the resin was washed with water (3 x 50 mL), methanol (3 x 50 mL), THF (3 x 50 mL) and methanol (3 x 50 mL) and then dried to give 8.3 g of resin **29** (118% of theoretical weight gain)

^{13}C - gel phase NMR (62.5 MHz, CDCl_3): δ = 155.0 (C1); 70.0 (framework); 68.7 ($-\text{CH}_2\text{CH}_2\text{OR}$); 64.3 ($-\text{CH}_2\text{CH}_2\text{OR}$); 61.6 (possible ($-\text{CH}_2\text{CH}_2\text{OH}$)); 50.4/50.0 (C2); 45.5-41.5 (resin anomaly); 29.1 (C3); 22.8, 17.0, 7.3 (framework).
IR = 1702 cm^{-1}
Br-analysis: 19.7%/19.6% ~ 1.2 mmol mustard/g (114%)

After 7 months:

^{13}C - gel phase NMR (62.5 MHz, CD_2Cl_2): δ = 156.3 (C1) 74.9 , 71.3 (framework) 70.0 ($-\underline{\text{CH}}_2\text{CH}_2\text{OR}$) 65.6 ($-\text{CH}_2\underline{\text{CH}}_2\text{OR}$) 62.8 ($-\text{CH}_2\underline{\text{CH}}_2\text{OH}$) 51.6/51.2 (C2) 46.7-42.0 (resin anomaly) 30.6 (C3) 24.1, 18.2, 8.5 (framework)
Br-analysis 19.3%/19.3% ~ 1.2 mmol mustard/g (114%)

Synthesis of resin-bound morpholine **30**

Versabeads O (2.7 g, 5 mmol, 1 equiv) was suspended in THF (40 mL). A solution of phosgene in toluene (20% w/w, 5.3 mL (ρ = 0.935 g/mL), 4.4 g phosgene, 10 mmol, 2 equiv) was added and the suspension was stirred at room temperature for 2 h. The solvent was removed and the resin was washed with THF (30 mL), methanol (2 x 30 mL) and THF (30 mL). The resin was suspended in THF (50 mL) and the suspension was cooled on an ice/water bath. Morpholine (3.0 g, 34 mmol, 7 equiv) was added slowly and the suspension was stirred at room temperature for 3.5 h. The suspension was filtered and the resin was washed with THF (3 x 50 mL), methanol (3 x 50 mL), water (3 x 50 mL) and THF (3 x 50 mL) and then dried.

^{13}C gel-phase NMR (62,5 MHz, CDCl_3): δ = 171.6 (resin impurity); 156,1 (C1); 72.5 ($-\underline{\text{CH}}_2\text{CH}_2\text{OH}$); 70.4 (framework); 69.5 ($-\text{CH}_2\underline{\text{CH}}_2\text{OR}$); 66.6 (C2); 65.3 ($-\text{CH}_2\underline{\text{CH}}_2\text{OR}$) 61.0 ($-\text{CH}_2\underline{\text{CH}}_2\text{OH}$); 43.9 (C3); 40.7, 23.5, 17.9, 8.0 (framework).

Synthesis of resin-bound bis(chloroethyl)amine **31** on a 0.15 mol scale with triethylamine as base

Versabeads O400 (75.6 g, 0.15 mol, 1 equiv) was suspended in THF (750 mL) and cooled on an ice/water bath. A solution of phosgene in toluene (20 % w/w, 160 mL (ρ = 0.935 g/mL), 29.5 g phosgene, 0.3 mol, 2 equiv) was added slowly and the suspension was stirred at room temperature for 2.5 h, then sucked dry. The resin was washed with THF (300 mL), methanol (2 x 300 mL) and THF (300 mL) and then suspended in a solution of bis(chloroethyl)amine, hydrochloride (134 g, 0.75 mol, 5 equiv) in water (300 mL). The suspension was cooled on an ice/water bath and triethylamine (310 mL (ρ = 0.73 g/mL), 228 g, 2.25 mol, 15 equiv) was added slowly and the suspension was stirred at room temperature for 4 h. The suspension was filtered and the resin was washed with THF (2 x 250 mL), methanol (2 x 250 mL), water (2 x 250 mL), THF (2 x 250 mL) and methanol and then dried to give 103 g (110 %) of resin **31** as white beads.

^{13}C gel-phase NMR (62.5 MHz, CDCl_3): δ = 155.4 (C1); 73.6, 70.2 (framework); 69.0 ($-\underline{\text{CH}}_2\text{CH}_2\text{OR}$); 66.5 (framework); 64.4 ($-\text{CH}_2\underline{\text{CH}}_2\text{OR}$); 63.3 (framework); 51.0/50.5 (C2); 43.1, 42.3 (framework); 41.6 (C3); 23.0, 20.6, 17.2, 7.5 (framework). (See appendix A – spectrum 2)

7.4.1.2 Optimization of mustard addition

Attempt to synthesise 29 with only 2 equivalents of bromomustard salt

Versabeads O400 (10 g, 19.1 mmol, 1 equiv) was suspended in THF (150 mL) and the suspension was cooled down on an ice bath. A solution of phosgene in toluene (20 % (w/w), 52 mL, (ρ = 0.935 g/mL), 9.7 g phosgene, 98 mmol, 5.1 equiv) was added slowly and the suspension was allowed to heat to room temperature. The suspension was stirred for 5 h, and then filtered and the resin was washed with THF (2 x 100 mL), methanol (2 x 100 mL), water (2 x 100 mL) and THF (2 x 100 mL).

The resin was then suspended in a solution of bis(bromoethyl)amine, hydrobromide (11.8 g, 93% (w/w), 35 mmol, 1.8 equiv) in water (80 mL) and cooled on an ice/water bath. Triethylamine (16 mL (ρ = 0.73 g/mL), 11.6 g, 110 mmol, 6 equiv) was added slowly and the suspension was stirred for 19 h. The suspension was sucked dry and the resin was washed with water (2 x 100 mL), THF (2 x 100 mL) and methanol (2 x 100 mL) and then dried.

End weight: 10.6 g (71 % of theoretical weight)

^{13}C gel-phase NMR (62.5 MHz, CDCl_3): 160.7 (possible cross linking) 155.4 (C1) 72.3 ($-\text{CH}_2\text{CH}_2\text{OH}$) 70.3 (framework) 69.0 ($-\text{CH}_2\text{CH}_2\text{OR}$) 64.6 ($-\text{CH}_2\text{CH}_2\text{OR}$) 62.7 (possible cross-linking) 61.4 ($-\text{CH}_2\text{CH}_2\text{OH}$) 50.7/50.3 (C2) 43.2; 41.1 (framework) 29.3 (C3) 23.0; 17.3; 7.5 (framework)

Estimated loading from ^{13}C gel-phase NMR: 56%
Br-analysis 11.8% ~ 0.75 mmol mustard/g (58%)

Attempted synthesis of 29 with 2 equivalents of bromomustard salt and heat

Versabeads O400 (7.0 g, 13.4 mmol, 1 equiv) was suspended in THF (70 mL) and the suspension was cooled down on an ice/water bath. A solution of phosgene in toluene (20 % (w/w), 15 mL, (ρ = 0.935 g/mL), 2.8 g phosgene, 28 mmol, 2.1 equiv) was added slowly, the ice/water bath was removed and the suspension was stirred for 2.5 h at room temperature

The suspension was sucked dry and the resin was washed with THF (50 mL), water (50 mL), THF (50 mL) and water (50 mL). The resin was then suspended in a solution of bis(bromomethyl)amine, hydrobromide (9.2 g, (92% (w/w), 27 mmol, 2 equiv) in water (40 mL) and cooled on an ice/water bath. A solution of potassium carbonate (5.5 g, 40 mmol, 3 equiv) in water (30 mL) was added slowly. The suspension was heated to 80°C and kept at this temperature overnight. The suspension was allowed to cool, then sucked dry and the resin was washed with THF (2 x 70 mL) methanol (2 x 70 mL) water (2 x 70 mL) and THF (2 x 70 mL) then dried. End weight: 6.3 g

^{13}C gel phase NMR (62.5 MHz, CDCl_3) was not different from Versabeads.

7.4.1.3 Resin 31 stability test

Resin **31** (3.0 g, 4.3 mmol, 1 equiv) was suspended in a solution of potassium carbonate (1.5 g, 11 mmol, 2.5 equiv) and potassium iodide (0.14 g, 0.87 mmol, 0.2 equiv) in water (15 mL) and heated to 80°C.

After 4 h a sample was removed for, washed with water and methanol and dried. ^{13}C -gel phase NMR (62.5 MHz, CDCl_3) showed no change from **31**.

After 21 h a sample was removed for NMR experiment, washed with water and methanol and dried. ^{13}C -gel phase NMR (62.5 MHz, CDCl_3) showed almost all mustard cleaved judged by peaks at 72.6 ppm and 61.2 ppm.

Screening of bases in the formation of 31 (Table 12)

General procedure: Versabeads O400 (2.0 g, 3.9 mmol, 1 equiv) were suspended in THF (20 mL) at room temperature. A solution of phosgene in toluene (20% (w/w), 4 mL ($\rho = 0.935 \text{ g/mL}$), 0.75 g phosgene, 7.6 mmol, 1.9 equiv) was added and the suspension was stirred at room temperature for 2.5 h and then sucked dry. The resin was washed with THF (20 mL), methanol (20 mL) and THF (20 mL), then suspended in water (10 mL). Bis(chloroethyl)amine, hydrochloride (1.4 g, 7.9 mmol, 2.0 equiv) was added, followed by base (23 mmol, 6 equiv). The suspensions were stirred for 4 h at room temperature and then filtered, and the resins were washed with water (2 x 10 mL), THF (2 x 20 mL), methanol (2 x 20 mL) and THF (2 x 20 mL) and then dried. Analyzed with ^{13}C gel phase NMR.

| Entry | base | Amount | NMR height (64 ppm) | NMR Peak height (61 ppm) | NMR conversion |
|-------|------------------------|----------------|---------------------|--------------------------|----------------|
| 1 | Triethylamine | 3.2 mL (2.4 g) | 59 mm | - | full |
| 2 | Potassium carbonate | 3.2 g | 55 mm | - | full |
| 3 | Pyridine | 1.9 mL (1.8 g) | - | 35 mm | none |
| 4 | Diisopropyl ethylamine | 2.4 mL (3.0 g) | 75 mm | - | full |

7.5 Synthesis of N-aryl piperazines

7.5.1 Initial experiments

7.5.1.1 Addition of aromatic nucleophiles to resin bound mustards **29** and **31** (Table 13)

Synthesis of resin bound 1-(4-fluorophenyl)piperazine (32)

Synthesis of resin-bound 1-(4-fluoropiperazine) **32 at room temperature in water**

Resin **29** (0.27 g, 0.18 mmol, 1 equiv) was suspended in water (2 mL) with potassium carbonate (77 mg, 0.56 mmol, 3 equiv). 4-fluoroaniline (0.17 g, 1.5 mmol, 8 equiv) was added and the suspension was agitated overnight.

The suspension was filtered and the resin was washed with water (2 x 2 mL), THF (6 x 2 mL), dichloromethane (6 x 2 mL) and methanol (2 x 2 mL) and then dried.

¹³C gel phase NMR (62.5 MHz, CD₂Cl₂): δ = 156.2 (C1); 119.1 (C2); 116.3 (C3) 79.7-74.4 (resin artefacts); 71.3 (framework); 67.2 (-CH₂CH₂OR); 65.4 (**30**); 62.2 (-CH₂CH₂OH) 51.0 (C4 + **29**); 44.9 (C5 + **30**) 30.4 (**29**) 21.5, 18.1 (framework)

¹⁹F gel phase NMR (470 MHz, CD₂Cl₂): δ -124.9 ppm

¹H MAS NMR: (500 MHz, CD₂Cl₂): New protons between 6.7 ppm and 7.0 ppm (aromat)

N elemental analysis: 1.01% ~ 0.72 mmol N/g

F elemental analysis: 0.35% ~ 0.18 mmol F/g (47%)

Synthesis of resin-bound 1-(4-fluoropiperazine) **32 on gram-scale at room temperature and attempted cleavage**

Versabeads O400 (17.4 g, 33.2 mmol, 1 equiv) were suspended in THF (200 mL). A solution of phosgene in toluene (20% (w/w), 120 mL (ρ = 0.935 g/mL), 22.4 g phosgene, 230 mmol, 6.8 equiv) was added slowly and the suspension was stirred at room temperature for 5 h. The suspension was sucked dry and the resin was washed with THF (2 x 100 mL), water (2 x 100 mL) and THF (100 mL).

The resin was suspended in a solution of bis(bromoethyl)amine, hydrobromide (70.3 g (93% (w/w), 65.4 g bis(bromoethyl)amine, hydrobromide, 210 mmol, 6.3 equiv). Triethylamine (87 mL (ρ = 0.73 g/mL), 64 g, 630 mmol, 19 equiv) was added slowly with cooling and the suspension was stirred at room temperature overnight. The suspension was sucked dry and the resin was washed with water (3 x 100 mL), THF (1 x 100 mL), water (2 x 100 mL) and THF (3 x 100 mL), to form resin **29**.

IR = 1701 cm⁻¹

The resin was suspended in THF (100 mL). 4-fluoroaniline (23 g, 210 mmol, 6.3 equiv) was added, followed by slow addition of potassium carbonate (14.7 g, 105 mmol, 2.5 equiv) in water (100 mL). The suspension was stirred for 21 h at room temperature, then sucked dry. The resin was washed with water (3 x 100 mL) and THF (3 x 200 mL), then with alternating THF (200 mL) and methanol (100 mL) until the washing was colorless. The resin was dried.

^{13}C gel phase NMR (62.5 MHz; CDCl_3): δ 159.1 (C1); 155.3 (C2); 147.5 (C3); 118.4 (C4); 115.5/115.2 (C5) 73.8 (framework) 72.3 ($-\text{CH}_2\text{CH}_2\text{OH}$); 70.3 (framework); 69.3, 69.0 ($-\text{CH}_2\text{CH}_2\text{OR}$) 66.2 (**30**); 64.5, 64.4 ($-\text{CH}_2\text{CH}_2\text{OR}$) 61.4 ($-\text{CH}_2\text{CH}_2\text{OH}$); 50.7; 50.2 (C6 + bromethylamine) 43.5 (C7) 43.2 (**30**) 42.3; 41.0 (framework); 29.3 (bromethylamine); 23.0; 17.2 (framework) 13.7 (artefact), 7.5 (framework).

Estimated conversion by relative heights of 43.5 ppm and 29.3 ppm ~ 30%.

The resin was suspended in THF (350 mL). Methanol was added (16.5 mL (ρ = 0.79 g/mL), 13 g, 0.42 mol, 10 equiv) and the suspension was cooled on an ice/water bath. Lithium borohydride (9.0 g, 0.42 mol, 10 equiv) was added. The suspension was heated to reflux and kept at this temperature overnight. The reaction was quenched through slow addition of acetone (150 mL), the suspension was filtered and the resin was washed with THF (4 x 100 mL), 1 M aqueous HCl (3 x 20 mL) and THF (100 mL). THF was removed through evaporation and the water phase was made basic with aqueous ammonia (50 mL, 25 % w/v) and extracted with diethyl ether (5 x 200 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (2 x 50 mL), brine (2 x 50 mL) and water (4 x 50 mL), dried (anhydrous sodium sulphate) and evaporated to give 1.72 g of a brown oil.

The oil was dissolved in 2-propanol (10 mL). Oxalic acid dihydrate (0.8 g, 6.3 mmol) was dissolved in 2-propanol and slowly added to give 2.07 g of white crystals.

^1H NMR (500 MHz, D_2O): δ = 2.81 (s, 3H, Me-); 2.93-3.05 (m, 2H, H1/H2); 3.05-3.20 (m, 2H, H1/H2); 3.40-3.70 (m, 4H, H3); 6.95-7.02 (m, 4H, H4).

^{13}C NMR (125 MHz, D_2O): δ = 164.4 (C1); 159.8 (C2); 145.3 (C3); 120.2 (C4); 116.4 (C5); 53.3 (C6); 48.4 (C7); 43.2 (C8).

LC/MS / UV_{254} showed two impurities with a mass of 292/306 amu

Free-base of the oxalate was made through suspension in aqueous ammonia (5 % w/v) and extraction with diethyl ether

^1H NMR (500 MHz, CDCl_3) of the free base contained double doublet at 2.88 ppm and 3.12 ppm, which correlates to ^{13}C NMR (125 MHz, CDCl_3) peaks at 44.7 ppm and 48.8 ppm. This corresponds to aliphatic peaks in the spectra of similar triamines in literature,²⁸¹ which makes it plausible that diaddition products **34/35** are formed (appendix A spectrum 3 and 4).

Attempted synthesis of **32** with heating

Resin **29** (7.25 g, 9.3 mmol, 1 equiv) was suspended in water (70 mL) with 4-fluoroaniline (5.2 g, 46.5 mmol, 5 equiv). A solution of potassium carbonate (3.2 g, 23 mmol, 2.5 equiv) in water (70 mL) was added slowly and the suspension was heated to reflux (100 °C) and kept at this temperature for 18 h. The suspension was filtered and the resin was washed with THF (3 x 100 mL), methanol (2 x 100 mL), water (2 x 100 mL), THF (2 x 100 mL) and acetone (3 x 100 mL) and then dried.

End weight: 5.86 g

¹³C gel phase NMR (62.5 MHz, CDCl₃): δ = 155.5 (C1); 148.5 (C2); 118.9 (C3); 116.0/115.7 (C4); 114.1 (diaddition product?); 74.4 (framework); 72.9 (-CH₂CH₂OH); 70.8 (framework); 64.9 (-CH₂CH₂OR); 61.9 (-CH₂CH₂OH); 50.6 (C5); 44.0/43.7 (C6 + framework); 41.3; 23.5; 17.7; 8.0 (framework).
Estimated cleavage from resin ~ 89%.

Resin-bound 4-fluoropiperazine (32) from 31 with heating

Resin **31** (1.5 g, 2.2 mmol, 1 equiv) was suspended in water (20 mL) with 4-fluoroaniline (1.2 g, 11 mmol, 5 equiv). A solution of potassium carbonate (0.75 g, 5.4 mmol, 2.5 equiv) was added and the suspension was heated to reflux and kept at reflux overnight. The suspension was filtered and the resin was washed with THF (2 x 20 mL), methanol (2 x 20 mL), water (2 x 20 mL) and THF (2 x 20 mL), and then dried.

¹³C gel phase NMR (62.5 MHz, CDCl₃): δ = 155.5 (C1); 147.5 (C2); 118.5 (C3); 115.4 (C4); 72.3 (-CH₂CH₂OH); 70.2 (framework); 64.4 (-CH₂CH₂OR); 61.3 (-CH₂CH₂OH); 50.0 (C5); 43.4/43.1 (C6 + framework); 41.6/40.8, 22.9, 17.2, 7.4 (framework).

Estimated cleavage from resin ~ 91%. (See appendix A - spectrum 3)

Attempt to form 32 with chloromustard, potassium iodide and heat (Table 13, entry 7)

Resin **31** (6.6 g, 9.5 mmol, 1 equiv) was suspended in water (30 mL) with 4-fluoroaniline (5.3 g, 48 mmol, 5 equiv) and cooled down on an ice/water bath. A solution of potassium carbonate (3.3 g, 24 mmol, 2.5 equiv) and potassium iodide (0.32 g, 1.9 mmol, 0.2 equiv) was added and the suspension was heated to 80 °C and stirred at this temperature for 23 h. The suspension was sucked dry and the resin was washed with water (2 x 50 mL), THF (2 x 50 mL), methanol (2 x 50 mL), THF (3 x 50 mL) then dried.

¹³C gel phase NMR (62.5 MHz, CDCl₃): δ = 155.0 (C1); 147.5 (C2); 118.2 (C3); 115.4 (C4); 113.1 (possible diaddition product); 72.2 (-CH₂CH₂OH); 70.2 (framework); 64.3 (-CH₂CH₂OR); 61.2 (-CH₂CH₂OH); 50.0 (C5); 43.4/43.1 (C6 + framework); 40.7, 26.8 (artefact), 22.9 (framework); 19.0 (artefact), 17.2, 7.4 (framework).

¹⁹F gel-phase NMR (470 MHz, CDCl₃): δ = - 123.7 ppm (**32**), -129.3 ppm (diaddition product?).

Estimated cleavage from resin ~ 87%.

Attempted synthesis of resin-bound 1-(4-iodophenyl)-piperazine and 1-(4-methoxyphenyl)-piperazine (table 13)

Attempted synthesis of 4-iodopiperazine 36 on resin and attempted cleavage to 37

Resin **29** (2 g, 2.4 mmol, 1 equiv) was suspended in a solution of 4-iodoaniline (2.6 g, 12 mmol, 5 equiv) and potassium carbonate (0.83 g, 6 mmol, 2.5 equiv) in a water/acetonitrile mixture (3:1, 20 mL) at room temperature. After 24 h the

suspension was filtered and the resin was washed with 1 M aqueous HCl (4 x 50 mL), 5% aqueous ammonia (5 x 50 mL), acetonitrile (3 x 50 mL), 1M aqueous HCl (4 x 50 mL), 5% aqueous ammonia (5 x 50 mL), MeCN (3 x 50 mL), THF (3 x 50 mL) and acetone (3 x 50 mL) and then dried.

^{13}C gel phase NMR (62.5 MHz, CD_2Cl_2): δ = 156.3 (C1); 138.5 (C2); 119.5 (C3); 115.8 (Most likely diaddition byproduct) 71.3 ($-\text{CH}_2\text{CH}_2\text{OH}$); 70.0 (framework); 67.9 ($-\text{CH}_2\text{CH}_2\text{OR}$); 65.6 ($-\text{CH}_2\text{CH}_2\text{OR}$); 62.3 ($-\text{CH}_2\text{CH}_2\text{OH}$) 51.2/50.1 (**29**) 49.5 (C4); 44.3 (C6); 30.5 (**29**); 24.1, 18.2, 8.4 (framework).

Estimated cleavage by peaks at 65.6 ppm and 62.3 ppm: 33%

The resin was suspended in THF (20 mL). Methanol (0.94 mL, (ρ = 0.79 g/mL) 0.74 g, 24 mmol, 10 equiv) and lithium borohydride (0.56 g, 26 mmol, 11 equiv) was added and the suspension was heated to reflux overnight. The reaction was quenched with acetone (30 mL) and filtered, then washed with 1 M aqueous HCl (200 mL), THF (200 mL), 1 M aqueous HCl (200 mL) and water (100 mL).

The filtrate was made basic with aqueous ammonia (25% w/v, 100 mL) and extracted with diethyl ether (4 x 150 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (2 x 100 mL), brine (2 x 100 mL) and water (2 x 100 mL), dried (anhyd sodium sulphate) and evaporated.

Yield: 41 mg of crude compound **37**.

^1H NMR (500 MHz, CDCl_3): δ = 2.23 (s, 3H, -Me); 2.54-2.57 (m, 4H, H1); 3.16-3.19 (m, 4H, H2); 6.68 (d, J = 8.9 Hz, 2H, H3); 7.50 (d, J = 9.0 Hz, 2H, H4)

Attempt to form **36** with heating

Resin **29** (1.5 g, 2.1 mmol, 1 equiv) was suspended in water (20 mL) with potassium carbonate (0.74 g, 5.4 mmol, 2.5 equiv). 4-iodoaniline (2.8 g, 13 mmol, 6 equiv) was purified by recrystallization from heptane, then dissolved in acetonitrile (20 mL) and added to the suspension, which was then heated to reflux (78°) and kept at this temperature for 21 h. The suspension was filtered and the resin was washed with THF (3 x 20 mL), methanol (3 x 20 mL), water (3 x 20 mL) and methanol (3 x 20 mL) and then dried.

^{13}C gel phase NMR (62.5 MHz, CD_2Cl_2) shows that almost all compound have been cleaved from resin (strong peaks at δ = 73.9 ($-\text{CH}_2\text{CH}_2\text{OH}$) and 62.8 ($-\text{CH}_2\text{CH}_2\text{OH}$)).

Attempt to form **38** (Table 13, entry 8)

Resin **29** (5.0 g, 6.4 mmol, 1 equiv) was suspended in water (35 mL) with 4-methoxyaniline (3.9 g, 32 mmol, 5 equiv). A solution of potassium carbonate (2.2 g, 16 mmol, 2.5 equiv) in water (15 mL) was added and the suspension was heated to 60 °C and kept at this temperature overnight. The suspension was sucked dry and the resin was washed with THF (3 x 50 mL), methanol (2 x 50 mL) water (2 x 50 mL) and THF (2 x 50 mL), then dried.

^{13}C gel phase NMR (62.5 MHz, CDCl_3): δ = 154.9 (C1); 154.0 (C2); 145.2 (C3); 118.6 (C4); 114.2 (C5); 73.9 (framework); 72.3 ($-\text{CH}_2\text{CH}_2\text{OH}$); 70.3 (framework);

69.3 (-CH₂CH₂OR); 64.3 (-CH₂CH₂OR); 61.3 (-CH₂CH₂OH); 55.2 (C6); 50.6 (C7); 43.6 (C8); 40.9, 23.0, 17.2, 7.5 (framework).
Estimated cleavage from resin ~ 55%.

Attempted synthesis of piperazines bearing nitrogen heterocyclic substituents (table 13)

Attempted synthesis of resin-bound 1-(2-pyridyl)-piperazine (39)

Resin **29** (0.75 g, 1.2 mmol, 1 equiv) was suspended in a mixture of 2-aminopyridine (0.57 g, 5 mmol, 5 equiv) and potassium carbonate (0.41 g, 3 mmol, 2.5 equiv) in water (15 mL). The suspension was agitated for 26 h then filtered, and the resin was washed with water (3 x 10 mL), THF (3 x 10 mL) and methanol (3 x 10 mL). This washing cycle was repeated until no trace of starting material was left in the washing by HPLC.

¹³C- gel phase NMR (62.5 MHz, CDCl₃) was not different from starting material.

Attempted synthesis of resin-bound 1-(pyrimidin-2-yl)-piperazine (40)

Resin **29** (1.2 g, 1.1 mmol, 1 equiv) was suspended in water (10 mL). Pyrimidin-2-ylamine (0.52 g, 5.3 mmol, 5 equiv) and potassium carbonate (0.35 g, 2.6 mmol, 2.5 equiv) was added and the suspension was agitated overnight. The suspension was filtered, and the resin was washed with THF (3 x 10 mL), methanol (3 x 10 mL) and THF (3 x 10 mL) and then dried.

¹³C- gel phase NMR (62.5 MHz, CD₂Cl₂) showed only negligible conversion (very small peaks at δ = 128-130 ppm).

Attempted synthesis of resin-bound 1-(pyrimidin-2-yl)-piperazine (40) with microwave heating

Resin **31** (0.55 g, 0.71 mmol, 1 equiv) was suspended in water (4 mL) with pyrimidin-2-ylamine (0.31 g, 3.3 mmol, 4.6 equiv) and potassium carbonate (0.24 g, 1.7 mmol, 2.5 equiv) in an Emrys Process Vial. The vial was closed and the suspension heated with microwaves (100 °C, 6 min). The suspension was filtered and the resin was washed with THF (3 x 10 mL), methanol (3 x 10 mL) water (3 x 10 mL) and methanol (1 x 10 mL) and then dried.

¹³C- gel phase NMR (62.5 MHz, CDCl₃) showed that mustard have been converted to morpholine **30** (δ = 66.3 ppm).

7.5.1.2 Optimization of addition to resin-bound mustard 31

Solvent screening process (Table 14)

Resin **31** (2.0 g, 2.9 mmol, 1 equiv) was suspended in solvent (20 mL; 1.DMF, 2. THF, 3. MIBK, 4. water, 5. 1-butanol, 6. ethanol, 7. dimethoxyethyl ether) with 4-methoxyaniline (1.8 g, 14.4 mmol, 5 equiv), potassium carbonate (0.99 g, 7.2 mmol,

2.5 equiv) and potassium iodide (0.10 g, 0.58 mmol, 0.2 equiv). The suspension was heated to 80 °C overnight. The resins were filtered, washed with water (20 mL) and THF (20 mL) and analyzed by ^{13}C gel phase NMR (CDCl_3).

Resin **38** from reaction 3 (2.0 g) and 7 (1.6 g) were suspended in THF (20 mL). Methanol (1.0 mL ($\rho = 0.79 \text{ g/mL}$), 0.81 g, 26 mmol) and lithium borohydride (0.56 g, 26 mmol) were added and the suspension were kept at reflux temperature overnight. The reaction was quenched with ethyl acetate (20 mL) and the suspensions were filtered, washed with THF (2 x 20 mL); 1M aqueous hydrochloric acid (2 x 20 mL); THF (20 mL) 1M aqueous hydrochloric acid (2 x 20 mL) and THF (20 mL) then dried. The filtrates were washed with ethyl acetate (20 mL) and made basic, then extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with saturated sodium bicarbonate (10 mL), brine (10 mL) and water (10 mL), dried (anhydrous sodium sulphate) and evaporated.

Crude yield 1: 290 mg 2: 40 mg.

1 gave satisfactory NMR spectrum for **45a**

Base screening (table 15)

Resin **31** (2.0 g, 2.9 mmol, 1 equiv) was suspended in MIBK (20 mL) with 4-methoxyaniline (1.8 g, 14.4 mmol, 5 equiv), base (1. pyridine (1.2 mL ($\rho = 0.978$), 1.1 g, 14.4 mmol, 5 equiv); 2. DIPEA (2.46 mL ($\rho = 0.755$), 1.9 g, 14.4 mmol, 5 equiv); 3. 4-dimethylaminopyridine (1.76 g, 14.4 mmol, 5 equiv)) and potassium iodide (0.10 g, 0.58 mmol, 0.2 equiv)). The suspensions were kept at reflux overnight, then filtered, washed with methanol (3 x 20 mL), water (3 x 20 mL), THF (20 mL) and methanol (20 mL) and then dried. The samples were analyzed by ^{13}C gel-phase NMR (62.5 MHz, CDCl_3).

1 and 2 gave complete reaction judge by ^{13}C gel-phase NMR

7.5.2 Synthesis and cleavage of *N*-aryl piperazine derivatives

7.5.2.1 Gram scale synthesis of *N*-Aryl and *N*-aryl-*N'*-methyl piperazines

Versabeads™ O400 (90.0 g, 177 mmol, 1 equiv) were suspended in THF (900 mL). A solution of phosgene in toluene (20% w/w, 190 mL ($\rho = 0.935$ g/mL), 355 mmol, 2.0 equiv) was slowly added and the suspension was stirred mechanically at room temperature for 2 h. The liquid was removed and the resin was washed successively with THF (750 mL), methanol (2×500 mL), and THF (900 mL).

Bis(chloroethyl)amine hydrochloride (110 g, 0.61 mol, 3.5 equiv) was dissolved in water (450 mL) and was added to the resin. The suspension was cooled on an ice-water bath and potassium carbonate (147 g, 1.06 mol, 6.0 equiv) was added portionwise with mechanical stirring. The ice-water bath was removed and the suspension was stirred for 6 h at room temperature. The resin was recovered by filtration and washed successively with water (3×500 mL), THF (3×500 mL), Methanol (3×500 mL), water (2×500 mL), THF (1 750 mL), and methanol (2×500 mL) before drying in vacuo to give 123.1 g (103% of theoretical weight gain) of resin **31**.

Cl analysis: 11.9% Cl 1.68 mmol/g bis(chloroethyl)amine/g resin, (113% of theoretical maximum loading).

^{13}C NMR (CDCl_3): $\delta = 155.4$ (C1); 73.8, 70.2 (framework); 69.0 ($-\text{CH}_2\text{CH}_2\text{OR}$); 66.7, 64.5 ($-\text{CH}_2\text{CH}_2\text{OR}$), 63.2, 50.9/50.5 (C2); 43.1 (C3); 42.3, 23.0, 20.6, 17.2, 7.5 (framework).

Resin-bound *N*-arylpiperazines **32**, **38**, **43** and **44**.

Resin **31** (10.0 g, 14.8 mmol, 1 equiv) was suspended in MIBK (75 mL) in the presence of the aniline (74 mmol, 5 equiv) and KI (0.5 g, 3 mmol, 0.2 equiv). Then pyridine (12.0 mL ($\rho = 0.978$ g/mL), 12 g, 0.15 mol, 10 equiv) was added and the suspension was heated to 100 °C with mechanical stirring. After the reaction time stated in table 15, the solvent was removed and the resin was washed successively with THF (3×100 mL), methanol (3×100 mL), water (3×100 mL) and THF (3×100 mL), and dried in vacuo to give the immobilized piperazines. Completion of the reactions was confirmed through ^{13}C gel-phase NMR spectroscopy (For an example of reaction monitoring see appendix, spectrum 5).

N-Aryl-*N'*-methylpiperazines **45a-d** (Table 15); General Procedure

The appropriate resin (14.8 mmol) was suspended in THF (100 mL). Then, lithium aluminium hydride (5.7 g, 0.15 mol, 10 equiv) was added as pellets and the suspension was heated at reflux for 19 h with mechanical stirring. The reaction was cooled on an ice-water bath, quenched by the sequential addition of water (6 mL), aqueous NaOH soln (13% w/v, 6 mL), and water (17 mL). The suspension was filtered and the resin was washed successively with THF (3×100 mL), 1 M aqueous HCl (3×100 mL), THF (1×60 mL), and 1 M aqueous HCl (2×100 mL).

The THF was removed from the filtrate under reduced pressure. The residual filtrate was washed with ethyl acetate (2×50 mL) and made basic with aqueous ammonia (25% w/v, 100 mL). The resulting suspension was shaken with toluene (100 mL) and filtered. The solid was washed with toluene (2×100 mL). The filtrate was separated and the aqueous phase was washed with toluene (3×100 mL). The combined organic phases were washed with sat. aqueous sodium bicarbonate (40 mL), brine (40 mL), and water (2×40 mL), dried (anhyd sodium sulphate), and evaporated.

1-(4-methoxyphenyl)-4-methylpiperazine (45a) ²⁴³

Red solid. Yield: 1.85 g (60%). Mp 63-65 °C

¹H NMR (500 MHz, CDCl₃): δ = 2.34 (s, 3 H, H1); 2.57 (t, J = 4.7 Hz, 4 H, H2); 3.10 (t, J = 5.2 Hz, 4 H, H3); 3.76 (s, 3 H, H4); 6.83 (ddd, J¹ = 10.4 Hz, J² = 9.0 Hz, J³ = 2.8 Hz, 2 H, H6); 6.90 (ddd, J¹ = 10.4 Hz, J² = 9.0 Hz, J³ = 2.3 Hz, 2 H, H6).

¹³C NMR (62.5 MHz, CDCl₃): δ = 154.2 (C1); 146.1 (C2); 118.5 (C3); 114.8 (C4); 55.9 (C5); 55.7 (C6); 51.0 (C7); 46.5 (C8).

Anal. Calcd for C₁₂H₁₈N₂O: C, 69.86; H, 8.80; N, 13.58. Found: C, 69.70; H, 8.88; N, 13.43.

1-Methyl-4-phenylpiperazine (45b) ²⁴³

Purified by flash chromatography (ethyl acetate-heptane-triethyl amine). Yellow oil; yield: 0.96 g (37%).

¹H NMR (500 MHz, CDCl₃): δ = 2.31 (s, 3 H, H1); 2.53 (t, J = 4.7 Hz, 4 H, H2); 3.18 (t, J = 4.7 Hz, 4 H, H3); 6.81-6.85 (m, 1 H, H4); 6.88-6.92 (m, 2 H, H5); 7.21-7.26 (m, 2 H, H6).

¹³C NMR (250 MHz, CDCl₃): δ = 151.7 (C1); 129.5 (C2); 120.1 (C3); 116.5 (C4); 55.6 (C5); 49.5 (C6); 46.6 (C7).

1-(4-Fluorophenyl)-4-methylpiperazine (45c)

Purified by flash chromatography (ethyl acetate-heptane-triethyl amine). Yellow solid; yield: 0.6 g (21%); mp 42-44 °C.

¹H NMR (500 MHz, CDCl₃): δ = 2.34 (s, 3 H, H1); 2.56 (t, J = 5.2 Hz, 4 H, H2); 3.12 (t, J = 5.2 Hz, 4 H, H3); 6.84-6.88 (m, 2 H, H4); 6.92-6.98 (m, 2 H, H5).

¹³C NMR (62.5 MHz, CDCl₃): δ = 158.5; 156.6 (C1); 148.3 (C2); 118.2; 118.1 (C3); 115.9; 115.8 (C4); 55.5 (C5); 50.5 (C6); 46.5 (C7).

Anal. Calcd for C₁₁H₁₅N₂F: C, 68.01; H, 7.78; N, 14.42. Found: C, 67.89; H, 7.89; N, 14.38.

1-(3,4-Dichlorophenyl)-4-methylpiperazine (45d)

Byproduct 1-(4-chlorophenyl)-4-methylpiperazine **47** was removed by Kugelrohr distillation at 160-165 °C (1 mbar), and the residue was purified by flash chromatography (ethyl acetate-heptane-triethyl amine).

Brown oil, which solidified upon standing; yield: 0.13 g (4%); mp 52-53 °C.

¹H NMR (500 MHz, CDCl₃): δ = 2.34 (s, 3 H, H1); 2.55 (t, J = 5.2 Hz, 4 H, H2); 3.18 (t, J = 4.7 Hz, 4 H, H3); 6.74 (dd, J¹ = 9.0 Hz, J² = 2.8 Hz, 1 H, H4); 6.95 (d, J = 2.8 Hz, 1 H, H5); 7.26 (d, J = 8 Hz, 1 H, H6).

¹³C NMR (62.5 MHz, CDCl₃): δ = 151.1 (C1); 133.1 (C2); 130.8 (C3); 122.4 (C4); 117.5 (C5); 115.6 (C6); 55.2 (C7); 49.0 (C8); 46.5 (C9).

Anal. Calcd for C₁₁H₁₄N₂Cl₂: C, 53.89; H, 5.76; N, 11.43. Found: C, 54.12; H, 5.97; N, 11.38.

N-Aryl piperazines 46a-d; General procedure

The appropriate resin (14.8 mmol) was suspended in DME (100 mL). Then, *potassium tert-butoxide* (3.7 g, 33 mmol, 2.2 equiv) was added and the suspension was heated at reflux temperature for 3 h. The suspension was filtered and washed successively with DME (3 × 100 mL), 1 M aqueous HCl (3 × 100 mL), DME (1 × 50 mL), 1 M aq HCl (3 × 100 mL), and DME (2 × 50 mL). The DME was removed from the filtrate under reduced pressure, and the residual filtrate was washed with ethyl acetate (2 × 50 mL) and made basic with aqueous ammonia (25% w/v, 100 mL). The aqueous phase was extracted with toluene (6 × 100 mL). The combined organic phases were filtered to remove impurities, washed with saturated aqueous sodium bicarbonate (50 mL), brine (50 mL), and water (2 × 50 mL), dried (anhyd sodium sulphate), and evaporated.

The crude products were dissolved in ethanol (10 mL) and a solution of oxalic acid dihydrate (1.1 equiv) in ethanol (9 mL) was added with stirring. The oxalate formed was allowed to precipitate in the fridge overnight. In the case of **46a**, the equivalents of acid were calculated based on the HPLC purity, otherwise they were calculated on the total weight of the crude product.

1-(4-Methoxyphenyl)piperazine Oxalate (**46a**)

Light-brown crystals; yield: 0.85 g (20%); mp 199-200 °C.

¹H NMR (500 MHz, D₂O): δ = 3.30-3.40 (m, 8 H, H1), 3.76 (s, 3 H, H2), 6.97 (ddd, J¹ = 10.8 Hz, J² = 3.8 Hz, J³ = 2.4 Hz, 2 H, H3), 7.08 (ddd, J¹ = 10.4 Hz, J² = 3.8 Hz, J³ = 2.4 Hz, 2 H, H4).

¹³C NMR (62.5 MHz, D₂O): δ = 166.4 (C1), 155.2 (C2), 143.8 (C3), 120.3 (C4), 115.3 (C5), 56.1 (C6), 48.5 (C7), 43.5 (C8).

Anal. Calcd for C₁₃H₁₈N₂O₅: C, 55.20; H, 6.49; N, 9.91. Found: C, 55.22; H, 6.48; N, 9.80.

1-Phenylpiperazine Oxalate (**46b**)

Light-brown crystals; yield: 0.64 g (17%); mp 167-169 °C.

¹H NMR (500 MHz, D₂O): δ = 3.35-3.43 (m, 8 H, H1), 7.03-7.07 (m, 1 H, H2), 7.08-7.12 (m, 2 H, H3), 7.34-7.39 (m, 2 H, H4).

¹³C NMR (62.5 MHz, D₂O): δ = 166.5 (C1), 149.9 (C2), 130.1 (C3), 123.0 (C4), 118.2 (C5), 47.3 (C6), 43.5 (C7).

Anal. Calcd for C₁₂H₁₆N₂O₄: C, 56.90; H, 6.77; N, 11.06. Found: C, 56.65; H, 6.49; N, 11.10.

1-(4-Fluorophenyl)piperazine Oxalate (**46c**)

Light-brown crystals; yield: 0.93 g (23%); mp 172-173 °C.

¹H NMR (500 MHz, D₂O): δ = 3.32-3.40 (m, 8 H, H1), 7.07-7.12 (m, 4 H, H2).

¹³C NMR (62.5 MHz, D₂O): δ = 166.3 (C1), 157.8 (C2), 146.3 (C3), 120.2/120.2 (C4), 116.4/116.2 (C5), 48.1 (C6), 43.5 (C7).

Anal. Calcd for C₁₂H₁₅N₂O₄F: C, 53.33; H, 5.59; N, 10.37. Found: C, 53.35; H, 5.68; N, 10.37.

1-(3,4-Dichlorophenyl)piperazine Oxalate (**46d**)

Recrystallized (2-propanol). Light-brown crystals; yield: 0.27 g (6%); mp 230-232 °C.

^1H NMR (500 MHz, D_2O): δ = 3.22-3.32 (m, 8 H, H1), 6.86 (dd, J^1 = 8.9 Hz, J^2 = 2.8 Hz, 1 H, H2), 7.11 (d, J = 2.8 Hz, 1 H, H3), 7.32 (d, J = 9.0 Hz, 1 H, H4).

^{13}C NMR (62.5 MHz, D_2O): δ = 149.7 (C1), 131.2 (C2), 119.1 (C3), 117.6 (C4), 46.7 (C5), 43.3 (C6).

Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_4\text{Cl}_2$: C, 44.81; H, 4.39; N, 8.71. Found: C, 45.21; H, 4.61; N, 8.58.

7.5.2.2 Nucleophilic cleavage to form carbamate 48

Resin **31** (10.0 g, 14.8 mmol, 1 equiv) was suspended in MIBK (100 mL). 4-Methoxyaniline (8.9 g, 75 mmol, 5 equiv) and KI (0.48 g, 3 mmol, 0.2 equiv) were added, followed by pyridine (6 mL, 75 mmol, 5 equiv). The mixture was heated to 100 °C for 15 h. The resin was washed successively with THF (2×100 mL), methanol (2×100 mL), water (2×100 mL), THF (2×100 mL), and methanol (2×100 mL), and then was suspended in Methanol (100 mL). Then, KOH (8.2 g, 140 mmol, 10 equiv) was added and the suspension was heated at reflux for 3.5 h. The suspension was filtered and the resin was washed successively with THF (2×100 mL), 1 M aqueous HCl (2×100 mL), THF (1×100 mL), 1 M aqueous HCl (2×100 mL), and THF (1×100 mL). The THF was removed by evaporation in vacuo and the remaining solution was washed with ethyl acetate (2×50 mL). The aqueous phase was made basic with aqueous ammonia (25 w/v, 25 mL) and extracted with diethyl ether (5×100 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (50 mL), brine (50 mL), and water (2×50 mL), dried (anhyd sodium sulphate), and evaporated to give compound **4** as an oil that solidified upon standing.

Yield: 1.15 g (32%); mp 94-97 °C.

^1H NMR (500 MHz, CDCl_3): δ = 3.00-3.04 (m, 4 H, H1), 3.59-3.65 (m, 4 H, H2), 3.73 (s, 3 H, H3), 3.77 (s, 3 H, H4), 6.84 (ddd, J^1 = 9.4 Hz, J^2 = 3.3 Hz, J^3 = 2.8 Hz, 2 H, H5), 6.90 (ddd, J^1 = 9.4 Hz, J^2 = 3.3 Hz, J^3 = 2.8 Hz, 2 H, H6).

^{13}C NMR (62.5 MHz, CDCl_3): δ = 156.3 (C1), 154.7 (C2), 146.0 (C3), 119.3 (C4), 114.9 (C5), 55.9 (C6), 53.0 (C7), 51.3 (C8), 44.3 (C9).

Anal Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.06; H, 7.30; N, 11.06.

7.5.2.3 Zinc borohydride mediated reductive cleavage of 44

Screening reaction

Resin **44** (1.0 g, 1.5 mmol, 1 equiv) was suspended in THF (10 mL) in an Emrys Process Vial (20 mL). ZnCl_2 (0.3 g, 2.3 mmol, 1.5 equiv) and sodium borohydride (0.17 g, 4.5 mmol, 3 equiv) was added, the vial was sealed and the reaction was heated with microwaves (110°C, 30 min). The suspension was filtered and the resin was washed with THF (2×20 mL), water (20 mL), THF (3×20 mL), 1M aqueous HCl (3×10 mL), THF (20 mL), 1M aqueous HCl (3×10 mL), THF (2×20 mL). THF was evaporated from the filtrate and the aqueous phase were washed with ethyl acetate (10 mL), and then made basic with aqueous ammonia (25% (w/v), 25 mL) and extracted with toluene (6×20 mL). The combined organic phases were washed with

saturated aqueous sodium bicarbonate (10 mL); brine (5 mL) and water (10 mL), dried (anhydrous sodium sulphate) and evaporated.

End weight 10 mg.

^1H NMR (500 MHz; CDCl_3) of crude product: Largest aromatic proton signals: δ = 7.25 (dd, 1H); 6.95 (d, 1 H); 6.84 (dd, 1H) corresponds to aromates from 1-(3,4 – dichlorophenyl)-4-methylpiperazine **45d**

No peaks from 1-(4-chlorophenyl)-4-methylpiperazine **47** (δ = 7.20 ppm and 6.84 ppm)

Methyl peaks at 2.34 ppm (main product); 2.27 and 2.71 (impurities, possibly boron complexes of product)

Distribution 2.34: 2.27: 2.71 ~ 5.9: 2.5: 3.1 ~ 51 % product **45d**.

Gram-scale cleavage of resin **44**

Resin **31** (10 g, 14 mmol, 1 equiv) was suspended in MIBK (75 mL) with 3,4-dichloroaniline (11.1 g, 69 mmol, 5 equiv) and potassium iodide (0.5 g, 3 mmol, 0.2 equiv). Pyridine (12.0 mL (ρ = 0.978 g/mL), 11.7 g, 150 mmol, 10 equiv) was added and the suspension was heated to 100 °C and stirred at this temperature for 112 h. The suspension was sucked dry and the resin was washed with THF (2 x 100 mL), ethanol (2 x 100 mL), water (2 x 100 mL) and ethanol (2 x 100 mL) then dried.

^{13}C gel phase NMR (62.5 MHz, CDCl_3) corresponded to resin **44**.

Resin **44** was suspended in THF (100 mL). Zinc chloride (5.8 g, 43 mmol, 3 equiv) and sodium borohydride (3.2 g, 85 mmol, 6 equiv) was added and the suspension was stirred for 3 h at reflux. The reaction was quenched with water (20 mL), and the suspension was filtered. The resin was washed with THF (2 x 50 mL), 1 M aqueous HCl (3 x 50 mL), THF (50 mL) and 1 M aqueous HCl (3 x 50 mL). THF was removed from filtrate by evaporation and the aqueous phase was washed with ethyl acetate (2 x 50 mL), and then made basic with aqueous ammonia (25 %, 100 mL). The aqueous phase was extracted with toluene (6 x 100 mL) and the combined organic phases were filtered, washed with saturated aqueous sodium bicarbonate (50 mL), brine (50 mL) and water (2 x 50 mL), then dried (anhydrous sodium sulphate) and evaporated.

70 mg of crude **45d** was isolated.

^1H NMR (500 MHz, CDCl_3): δ = 2.3 (s, 3H, H1); 2.5 (m, 4H, H2); 3.2 (m, 4H, H3) 6.5 – 7.5 (Aryl, No peaks from **47**)

LC/MS showed no **47**

The resin was suspended in 4M aqueous hydrochloric acid (100 mL) overnight to remove salts, washed with water (2x100 mL) and ethanol (2 x 100 mL) then dried.

^{13}C gel phase NMR (62.5 MHz, CDCl_3) still contained peaks from resin-bound compound **44** (peak at δ = 43 ppm).

7.5.2.4 Synthesis of the drug Sifaprazine (50)

Condition screening for Sifaprazine

Resin **31** (1.0 g, 1.5 mmol, 1 equiv) was suspended in MIBK (7 mL) with 2-benzylaniline (1.36 g, 7 mmol, 5 equiv), pyridine (1.25 mL ($\rho = 0.978$ g/mL), 1.2 g, 15 mmol, 10 equiv) and potassium iodide in an Emrys Process Vial (20 mL). The vial was sealed and the suspension was heated with microwave (150°C, 2 h). The suspensions were filtered and the resins were washed with THF (3 x 10 mL); ethanol (3 x 10 mL); water (3 x 10 mL) and THF (3 x 10 mL) and then dried.

| entry | Potassium iodide added (g) | equiv KI | conversion by ^{13}C NMR (43 ppm vs. 41 ppm) |
|-------|----------------------------|----------|-------------------------------------------------------|
| 1 | 0.05 | 0.2 | < 10 % |
| 2 | 0.75 | 3.0 | complete |

Resin from Entry 2 was suspended in 1 M lithium aluminium hydride in THF (7 mL, 7 mmol, 4.7 equiv) in an Emrys Process Vial (20 mL). The vial was sealed and the suspension was heated with microwave (90 °C, 15 min).

The suspension was filtered and the filtrate was quenched with water (10 ml). The resin was washed with THF (3 x 10 mL); 1M aqueous HCl (3 x 10 mL), THF (10 mL), 1M aqueous HCl (3 x 10 mL) and THF (2 x 10 mL).

THF were evaporated from the filtrate, and the filtrate was washed with ethyl acetate (2 x 10 mL). The aqueous phase was made basic with aqueous ammonia (25 % w/v; 20 mL) and extracted with toluene (6 x 10 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (5 mL) and water (5 mL), dried (anhydrous sodium sulphate) and evaporated.

^{13}C gel phase NMR of resin showed complete cleavage (No peak at 64 ppm)

^1H NMR (500 MHz, CDCl_3): 2.34 (s, H1); 2.55 (m, H2); 2.88 (m, H3); 4.07 (s, H4); 7.0-7.3 (aryl)

Gram scale Sifaprazine synthesis

Resin **31** (5.1 g, 7.5 mmol, 1 equiv) was suspended in MIBK (40 mL) with 2-benzylaniline (6.87 g, 37 mmol, 5 equiv) and potassium iodide (3.74 g, 22.5 mmol, 3 equiv). Then, pyridine (6 mL ($\rho = 0.978$ g/mL), 5.6 g, 71 mmol, 9.5 equiv) was added and the suspension was heated to 100 °C for 67 h with magnetic stirring. The resin was washed successively with NMP (3 x 50 mL), THF (3 x 50 mL), Methanol (3 x 50 mL), H_2O (3 x 50 mL), NMP (3 x 50 mL), THF (3 x 50 mL), Methanol (3 x 50 mL), and THF (3 x 50 mL), and then dried. The resin was suspended in THF (50 mL). Pellets of LiAlH_4 (2.8 g, 75 mmol, 10 equiv) were added and the suspension was refluxed for 19 h with magnetic stirring. The suspension was cooled on ice and quenched by the sequential addition of water (3 mL), aqueous NaOH (13% w/v, 3 mL), and water (10 mL). The suspension was filtered and the resin washed successively with THF (3 x 50 mL), 1 M aqueous HCl (3 x 50 mL), THF (1 x 50 mL), 1 M aqueous HCl (3 x 50 mL), and THF (3 x 50 mL). The filtrate was filtered

through Celite and the THF was removed under reduced pressure. The aqueous phase was made strongly acidic with conc. HCl and was washed with ethyl acetate (2 × 25 mL). The aqueous phase was then made basic with aqueous ammonia (25% w/v, 50 mL). The resulting suspension of salts was shaken with toluene (50 mL) and filtered. The solid was washed with toluene (2 × 50 mL). The filtrate was separated and the aqueous phase was washed with toluene (3 × 50 mL). The combined organic phases were washed with sat. aqueous sodium bicarbonate (25 mL), sat. aq NaCl (25 mL), and H₂O (2 × 40 mL), dried (anhyd. sodium sulphate), and evaporated to give a brown oil (134 mg). Purification through automated flash chromatography (ethyl acetate-heptane-triethylamine) yielded **50** as a slightly yellow oil that solidified upon standing.

Yield: 53 mg (2.7%), mp 77-79 °C.

¹H NMR (500 MHz, CDCl₃): δ = 2.34 (s, 3 H), 2.39-2.74 (m, 4 H), 2.89 (t, J = 4.8 Hz, 4 H), 4.07 (s, 2 H), 7.08-7.28 (m, 9 H).

¹³C NMR (62.5 MHz, CDCl₃): δ = 152.0 (C1), 142.2 (C2), 137.0 (C3), 131.3 (C4), 129.4 (C5), 128.7 (C6), 127.5 (C7), 126.1 (C8), 124.4 (C9), 121.0 (C10), 56.1 (C11), 53.0 (C12), 46.6 (C13), 37.0 (C14).

Anal Calcd for C₁₈H₂₂N₂: C, 81.16; H, 8.33; N, 10.20. Found: C, 80.72; H, 8.37; N, 10.46.

7.5.2.5 Attempted synthesis of N-aryl piperazines from sterically hindered anilines on resin (table 16)

2,6 – methyl aniline and resin 31

Resin **31** (10.0 g; 15 mmol; 1 equiv) was suspended in 75 mL MIBK with 2,6 – dimethylaniline (9.0 g; 74 mmol; 5 equiv); potassium iodide (0.5 g; 3 mmol; 0.2 equiv) and pyridine (12 mL; (ρ=0.978 g/mL); 5.9 g; 74 mmol; 10 equiv) and heated to 100 °C for 6 days.

Approximate conversion: (44 ppm/(41 ppm + 43 ppm))= 0.25.

2,6 – methyl aniline and resin bound mustard with microwave heating

Resin **31** (2 g, 3 mmol, 1 equiv) was suspended in MIBK (15 mL) with 2,6-dimethylaniline (1.9 g, 15 mmol, 5 equiv), pyridine (2.5 mL (ρ=0.978 g/mL), 2.4 g, 30 mmol, 10 equiv) and potassium iodide (0.1 g, 0.6 mmol, 0.2 equiv) in an Emrys Process Vial (20 mL). The vial was sealed and the suspension was heated with microwaves (150 °C, 6 h). The suspension was filtered and the resin was washed with THF (3 x 20 mL), ethanol (3 x 20 mL), water (3 x 20 mL) and THF (3 x 20 mL) then dried.

¹³C gel-phase NMR (62.5 MHz, CDCl₃) showed complete conversion (no peak at 41 ppm) but a complicated mixture of signals.

The resin was suspended in DME (17 mL) in an Emrys Process Vial (20 mL). Potassium *tert*-butoxide (0.67 g, 6 mmol, 2 equiv) was added and the vial was sealed. The suspension was heated with microwaves (110 °C, 1 h) and filtered. The resin was washed with DME (3 x 20 mL), 1 M aqueous HCl (3 x 20 mL), DME (1 x 20 mL), 1 M aqueous HCl (3 x 20 mL) and DME (2 x 20 mL).

Organic solvent were removed from the filtrate through evaporation and the acidic water phase was washed with ethyl acetate (2 x 10 mL). The water phase was made basic with aqueous ammonia (25% (w/v), 20 mL) and extracted with toluene (6 x 20 mL), the combined organic phases were washed with saturated aqueous sodium bicarbonate (20 mL); brine (20 mL) and water (2 x 20 mL), dried (anhyd sodium sulphate) and evaporated.

Yield: 10 mg. (< 2 %)

LC/MS showed 1 major product at 188 amu (Expected piperazine at 190 amu)

¹H NMR (500 MHz, CDCl₃): Mixture of products – possible piperazine at 2.2-2.4 ppm and 3.0-3.3 ppm

2,6- methoxyaniline and resin bound mustard

Resin **31** (0.75 g, 1.1 mmol, 1 equiv) was suspended in MIBK (5 mL) with 2,6 – methoxyaniline (0.85 g, 5.5 mmol, 5 equiv), potassium iodide (38 mg, 0.22 mmol, 0.2 equiv) and pyridine (0.9 mL (ρ=0.978 g/mL), 0.92 g, 12 mmol, 11 equiv) was added and the suspension was heated with microwave (150 °C, 1 h). The suspension was filtered and the resin was washed with THF (3 x 10 mL), ethanol (3 x 10 mL), water (3 x 10 mL) and ethanol (3 x 10 mL), then dried.

¹³C gel-phase NMR (62.5 MHz, CDCl₃) major peak at 41.6 ppm (-CH₂CH₂Cl)
Approximate conversion: (43 ppm/(41 ppm + 43 ppm)) = 15 mm/ (15mm + 110 mm) = 0.12

7.5.3 Scale-up and reuse of resin

7.5.3.1 Initial Experiments

Microwave screening experiments for lowering the aniline excess (Table 17)

Resin **31** (1.0 g, 1.4 mmol, 1 equiv) was suspended in MIBK (7mL) in an Emrys Process Vial (20 mL) with 4-methoxyanilin, potassium iodide and pyridine. Vessel was sealed and the contents were heated with microwaves (150 °C, 1 h). The suspensions were filtered and the resins were washed with THF (2 x 20 mL), ethanol (2 x 20 mL), water (2 x 20 mL) and THF (2 x 20 mL) and then dried.

Conversion measured through ¹³C gel-phase NMR (62.5 MHz, CDCl₃)

Cleavage of resin 38 from Table 17, entry 1 to form 45a

Resin **38** was suspended in 1 M lithium aluminium hydride in THF (10 mL, 10 mmol, 4.2 equiv) in an Emrys Process Vial (20 mL). When initial gas development had subsided the suspension was covered with nitrogen, the vial was sealed and the suspension was heated with microwaves (100 °C, 15 min). The suspension was filtered and the resin was washed with THF (3 x 10 mL), water (3 x 10 mL), 1M aqueous HCl (3 x 10 mL), THF (1x10 mL), 1M aqueous HCl (3x10 mL) and THF (2 x 10 mL) and then dried.

¹³C gel-phase NMR (62.5 MHz, CDCl₃) showed complete cleavage of carbamate linker from resin.

THF was evaporated from the filtrate and the aqueous phase was made basic with aqueous ammonia (25 % w/v, 10 mL). The precipitated salts were removed by filtration and the crystals were washed with toluene (2 x 10 mL). The aqueous phase of the filtrate was extracted with toluene (2 x 10 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (10 mL) and water (10 mL) and then dried (anhyd sodium sulphate) and evaporated to give 64 mg (32%) of **45a**.

¹H NMR (500 MHz, CDCl₃): δ = 2.34 (s, 3H, H1); 2.55-2.60 (m, 4H, H2); 3.07-3.11 (m, 4H, H3); 3.76 (s, 3H, H4); 6.83 (d, J = 9.2 Hz, 2H, H5); 6.90 (d, J = 9 Hz, H6).

¹³C NMR (125 MHz, CDCl₃): δ = 154.2; 146.1; 118.5; 114.8; 55.9; 55.7; 51.0; 46.5.

Test of the optimized conditions and resin reuse

First run of reaction

Versabeads VO400 (29 g, 54 mmol, 1 equiv) was suspended in THF (200 mL) and heated to 50 °C. Triphosgene (8.0 g, 27 mmol, 1.5 equiv) was dissolved in THF (100 mL) and added slowly. The suspension was stirred for 2 h. The solvent was removed and the resin was washed successively with THF (250 mL) ethanol (2 x 150 mL) and THF (250 mL). The resin was resuspended in a solution of bis(chloroethyl)amine, hydrochloride (14.5 g, 81 mmol, 1.5 equiv) in water (150 mL) and a solution of potassium carbonate (30 g, 216 mmol, 4 equiv) in water (150 mL) was added slowly. The resulting suspension was stirred for 5 h at room temperature, then sucked dry and the resin was washed with THF (2 x 250 mL), ethanol (2 x 150 mL), water (2 x 150 mL) and THF (2 x 250 mL) then dried to yield resin **31**.

Cl-analysis: 10.2 % ~ 2.9 mmol Cl/g ~ 1.4 mmol compound/g

¹³C gel-phase NMR (62.5 MHz, CDCl₃): δ = 155.3 (C1) 70.2 (framework) 68.9 (CH₂CH₂OR) 64.4 (CH₂CH₂OR) 50.9/50.4 (C2) 43.0 (framework) 41.5 (C3) 22.9, 17.1, 7.4 (framework)

Resin **31** (10.0 g, 14 mmol, 1 equiv) was suspended in MIBK (75 mL) with 4-methoxyaniline (3.4 g, 28 mmol, 2 equiv) and potassium iodide (9.3 g, 56 mmol, 4 equiv) and heated to 100 °C. Pyridine (6 mL (ρ = 0.978 g/mL), 5.6 g, 71 mmol, 5 equiv) was added slowly. The reaction was stirred for 28 h, then solvent was removed and the resin was washed with THF (3 x 100 mL), ethanol (2 x 100 mL); water (2 x 100 mL) and ethanol (2 x 100 mL), then dried to give resin **38**.

The resin was suspended in THF (40 mL) and cooled on an ice/water bath. 1M lithium aluminium hydride in THF (60 mL, 60 mmol, 4.2 equiv) was added and the suspension was heated at reflux for 4 h. The reaction was quenched with water (10 mL), then the suspension was filtered and the resin was washed with THF (3 x 50 mL), 1M aqueous HCl (2 x 50 mL), THF (1 x 50 mL), 1M HCl (3 x 50 mL) and THF (2 x 50 mL). THF was removed from the filtrate in vacuo and the solution was washed with ethyl acetate (2 x 50 mL). The water phase was made basic with aqueous NH₃ (200 mL, 25% w/v) and extracted with toluene (5 x 100 mL) The combined organic phases were washed with saturated sodium bicarbonate solution (50 mL) saturated aqueous NaCl- solution (50 mL) and water (2 x 50 mL), dried with 30 g anhydrous sodium sulphate, filtered and evaporated. Yield: 1.13 g (39%) of **45a**.

¹H-NMR: (500 MHz; CDCl₃) 2.35 (s, 3H, H1) 2.58 (4H, m, H2) 3.10 (4H, m, H3) 3.76 (3H, s H4) 6.83 (2H, ddd, (J₁=10.3 Hz; J₂=3.3 Hz; J₃=2.8 Hz) H5) 6.90 (2H, ddd (J₁=10.4 Hz; J₂=3.7 Hz; J₃=2.8 Hz) H6)

¹³C-NMR (250 MHz, CDCl₃): 154.2 (C1) 146.1 (C2) 118.5 (C3) 114.8 (C4) 56.0 (C5) 55.7 (C6) 51.0 (C7) 46.5 (C8)

Anal calcd for C₁₂H₁₈N₂O: C, 69.86 H, 8.80 N, 13.58 Found C, 69.99 H, 9.04 N, 13.56.

¹³C gel-phase NMR of resin showed no trace of peaks from **38**.

The resin was suspended overnight in 4 M aqueous HCl (100 mL), filtered, washed with water (2 x 100mL) and ethanol (2 x 100 mL), then dried.

End weight: 5.7 g (10.6 mmol) Yield 76 % of theory

Second run of reaction (resin reuse)

The previously used Versabeads (5.7 g, 10.6 mmol, 1 equiv) was suspended in THF (40 mL). The suspension was heated to 50°C. A solution of triphosgene (1.6 g, 5.3 mmol, 1.5 equiv) in 10 mL THF was added and the suspension was stirred for 2 h at 50 °C then cooled down and washed successively with THF (1 x 50 mL), ethanol (2 x 50 mL) and THF (1 x 50 mL). The resin was suspended in a solution of bis(chloroethyl)amine, hydrochloride (2.8 g, 16 mmol, 1.5 equiv) in water (30 mL) and a solution of potassium carbonate (6 g, 42 mmol, 4 equiv) in water (30 mL) was added slowly. The resulting suspension was stirred for 5 h at room temperature, then sucked dry and the resin was washed with THF (2 x 60 mL), ethanol (2x30 mL), water (2 x 30 mL) and THF (2 x 60 mL) then dried to give resin **31**.

¹³C gel phase NMR(62.5 MHz ; CDCl₃): 155.3 (carbonyl) 70.2 (framework) 68.9 (CH₂CH₂OR) 64.4 (CH₂CH₂OR) 50.9 50.4 (NCH₂CH₂Cl) 43.0 (framework) 41.5 (NCH₂CH₂Cl) 22.9, 17.1, 7.4 (framework, methyl and ethyl)
Cl – analysis: 10.3 % ~ 2.9 mmol Cl/g ~ 1.4 mmol/g

Resin **31** (6.0 g, 8.5 mmol, 1 equiv) was suspended in MIBK (45 mL) with 4-methoxyaniline (2.15 g, 17 mmol, 2 equiv) and potassium iodide (5.6 g, 34 mmol, 4 equiv) and heated to 100°C. Pyridine (2.85 mL (ρ = 0.978 g/mL), 2.8 g, 34 mmol, 4 equiv) was added slowly. The reaction was stirred for 28 h, then solvent was removed and the resin was washed with THF (3 x 60 mL), ethanol (2 x 60 mL), water (2 x 60 mL) and ethanol (2 x 60 mL), then dried to give resin **38**.

¹³C gel-phase NMR (62.5 MHz, CDCl₃): 153.8 (carbonyl) 144.8 (C1) 127.7 (C2) 118.4 (C3) 113.9 (C4) 69.9 (framework) 64.0 (CH₂CH₂OR) 60.9 (CH₂CH₂OH) 55.0 (MeO-) 50.3 (NCH₂) 43.2 (NCH₂) 22.6; 17.0; 7.3 (framework, methyl and ethyl)

Resin **38** was suspended in THF (25 mL) and cooled on an ice/water bath. 1M lithium aluminium hydride in THF (35 mL, 35 mmol, 4.1 equiv) was added and the suspension was heated to reflux for 4 h. The reaction was quenched with water (10 mL), then filtered and washed with THF (3 x 30 mL), 1 M aqueous (3 x 30 mL) HCl; THF (1 x 30 mL), 1M aqueous HCl (3 x 30 mL) and THF (2 x 30 mL). THF was removed from the filtrate in vacuo and the solution was washed with ethyl acetate (2 x

20 mL). The water phase was made basic with aqueous ammonia (25% w/v, 10 mL) and extracted with 60 mL toluene, then filtered. Precipitate was washed with toluene (2 x 60 mL). The water phase was separated from the filtrate and extracted with toluene (3 x 60 mL). The combined organic phases were washed with saturated sodium bicarbonate solution (20 mL), brine (20 mL) and water (2 x 20 mL), dried with 30 g anhydrous sodium sulphate, filtered and evaporated. Yield: 0.66 g (38%) of **45a**.

¹H-NMR (CDCl₃, 500 MHz): 2.35 (s, 3H, H1) 2.58 (4H, m, H2) 3.10 (4H, m, H3) 3.76 (3H, s H4) 6.83 (2H, ddd, (J₁=10.4 Hz; J₂=3.8 Hz; J₃=2.3 Hz) H5) 6.90 (2H, ddd (J₁=10.3 Hz; J₂=3.7 Hz; J₃=2.3 Hz) H6)

¹³C-NMR (250 MHz, CDCl₃): 154.2 (C1) 146.1 (C2) 118.5 (C3) 114.8 (C4) 56.0 (C5) 55.7 (C6) 51.0 (C7) 46.5 (C8)

Anal. Calcd. for C₁₂H₁₈N₂O: C, 69.86; H, 8.80; N, 13.58, Found: C, 69.78; H, 8.80; N, 13.38.

Large-scale (0.19 mol) synthesis of **45a** on Versabeads

Versabeads O400 (100 g, 0.19 mol, 1 equiv) was suspended in THF (750 mL) and heated to 50 °C. A solution of triphosgene (25 g, 84 mmol, 1.5 equiv) in THF (250 mL) was added and the suspension was stirred for 3 h. The solvent was removed and the resin was washed successively with THF (500 mL), ethanol (2 x 500 mL) and THF (500 mL). The resin was then suspended in a solution of bis(chloroethyl)amine, hydrochloride (50 g, 0.28 mol, 1.5 eq) in water (250 mL). The suspension was cooled on an ice/water bath and a solution of potassium carbonate (103 g, 0.74 mol, 4 equiv) in water (250 mL) was added slowly. The suspension was stirred at room temperature for 4 h. The solvent was removed with the suction tube and the resin was washed with THF (2 x 500 mL), ethanol (2 x 500 mL), water (3 x 500 mL), THF (500 mL) and ethanol (500 mL) then dried to give 139 g (124 %) of resin **31** (Cl- analysis: 12.3 % ~ 123 % of theory).

¹³C gel-phase NMR (62.5 MHz, CDCl₃) showed complete reaction (no peak at 61 ppm)

The resin was suspended in MIBK (1 l) with 4-methoxyanilin (45.8 g, 0.37 mol, 2 equiv) and potassium iodide (124 g, 0.74 mol, 4 equiv) and heated to 100°C. Pyridine (63 mL (ρ = 0.978 g/mL), 59 g, 0.74 mol, 4 equiv) was added slowly. Reaction was stirred for 28 h, filtered and washed THF (2 x 700 mL), ethanol (2 x 700 mL), water (3 x 700 mL), THF (2 x 700 mL), ethanol (1 x 700 mL), water (1 x 700 mL), ethanol (2 x 700 mL) and then dried to give resin **38**. (¹³C gel-phase NMR (62.5 MHz, CDCl₃): 154.9 (C1); 153.9 (C2); 145.1 (C3); 118.5 (C4); 114.1 (C3); 55.2 (C6); 50.5 (C7); 43.5 (C8))

The resin was suspended in 800 mL THF and cooled to -36 °C on a dry ice/diglyme bath. Lithium aluminium hydride was added as a 1 M solution in THF (880 mL, 0.88 mol, 4.7 equiv). The resulting suspension was heated at reflux for 5 h then cooled down. The reaction was quenched through slow addition of ethyl acetate (250 mL).

The resin was filtered and washed with THF (3 x 500 mL). The filtrate was concentrated in vacuo. The resin was further washed with 1 M aqueous HCl (3 x 500 ml) and THF (250 mL) and the pH of the second batch of filtrate was adjusted to 1 with 100 mL conc. HCl and combined with the first filtrate. The combined filtrates

were washed with ethyl acetate (2 x 200 mL), then made basic with aqueous ammonia (25% w/v, 600 mL). The resulting suspension was shaken with 300 mL toluene and then filtered. The precipitate was washed with toluene (2 x 300 mL). The combined filtrates were separated in organic and aqueous phases and the aqueous phase were extracted with toluene (3 x 300 mL). The combined organic phases were washed with saturated sodium bicarbonate solution (2 x 100 mL), brine (2 x 100 mL) and water (2 x 100 mL), dried with 150 g anhydrous sodium sulphate, filtered and evaporated to yield 21 g of **45a** which gradually turned red upon standing. Overall yield from unloaded Versabeads: 55%.

m.p. 65.9°C-67.3°C

¹H-NMR (500 MHz, CDCl₃): 2.34 (s, 3H); 2.56-2.58 (m, 4H); 3.09-3.11 (m, 4H); 3.76 (s, 3H); 6.83 (dd, J₁ = 10.3 Hz, J₂ = 3.8 Hz, 2H); 6.90 (dd, J₁ = 10.4 Hz, J₂ = 3.7 Hz, 2H).

¹³C-NMR (250 MHz, CDCl₃): 46.5; 51.0; 55.7; 55.9; 114.8; 118.5; 146.1; 154.2.

Anal calcd for C₁₂H₁₈N₂O: C, 69.86; H, 8.80; N, 13.58 found C, 69.95; H, 8.79; N, 13.57.

7.6 Synthesis of an imidazolidin-2-one by cyclative cleavage

7.6.1 Preliminary experiments

7.6.1.1 Initial investigation (Table 18)

Resin **31** (2.0 g, 2.6 mmol, 1 equiv) was suspended in water (20 mL) with 4-methoxyaniline (1.7 g, 14 mmol, 5.3 equiv), potassium carbonate (1.0 g, 7 mmol, 2.5 equiv) and potassium iodide (1. (0.1 g, 0.6 mmol, 0.2 equiv); 2. (0.46 g, 2.8 mmol, 1 equiv)). The suspension was heated to 80 °C and kept at this temperature for 23 h. The suspension was filtered and the resin was washed with water (3 x 20 mL), THF (3 x 20 mL), methanol (3 x 20 mL), water (20 mL) and methanol (2 x 20 mL).

The organic solvent was removed from the filtrate in vacuo, and the remaining aqueous phase was made strongly basic with aqueous ammonia (25% w/v, 20 mL), and extracted with ethyl acetate (6 x 20 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (10 mL), brine (10 mL) and water (2 x 10 mL), dried (anhydrous sodium sulphate) and evaporated. The resulting brown residue was purified through automated flash chromatography (ethylacetate/heptan).

Yield (1): 0.32 g (36 %):

¹H NMR (500 MHz, CDCl₃): δ = 3.30 (t, J = 6.1 Hz, 2H, H1); 3.50 (dd, (J₁ = 6.1 Hz, J₂ = 8.1 Hz), 2H, H2); 3.55 (t, J = 6.9 Hz, 2H, H3); 3.73 (s, 3H, H4); 3.76 (dd, (J₁ = 7.5 Hz, J₂ = 9.8 Hz) 2H, H5); 3.79 (s, 3H, H6); 6.60 (d, J = 9 Hz, 2H, H7); 6.77 (d, J = 8.9 Hz, 2H, H8); 6.89 (d, J = 9.0 Hz, 2H, H9); 7.43 (d, J = 8.9 Hz, 2H, H10)

Anal calc for C₁₉H₂₂N₃O₃: C, 66.84 H, 6.79 N, 12.31 found C, 66.75 H, 6.84 N, 12.22

Yield (2): 0.37 g (42 %):

¹H NMR (500 MHz, CDCl₃): δ = 3.30 (t, J = 6.1 Hz, 2H, H1); 3.50 (dd, (J₁ = 6.1 Hz, J₂ = 8.1 Hz), 2H, H2); 3.56 (t, J = 6.9 Hz, 2H, H3); 3.73 (s, 3H, H4); 3.76 (dd, (J₁ = 7.5 Hz, J₂ = 9.5 Hz) 2H, H5); 3.79 (s, 3H, H6); 6.60 (d, J = 9 Hz, 2H, H7); 6.77 (d, J = 8.9 Hz, 2H, H8); 6.89 (d, J = 9.1 Hz, 2H, H9); 7.43 (d, J = 9 Hz, 2H, H10)

Anal calc for C₁₉H₂₂N₃O₃: C, 66.84 H, 6.79 N, 12.31 Found C, 66.70 H, 6.91 N, 12.63

Other residues from entry 2:

Fraction 3 (Mix of hydrolysis products **41** and **53**): ¹H NMR (500 MHz, CDCl₃): δ = 3.30 (t, J = 5.6 Hz, 2H, **41**, H1); 3.40-3.46 (m, 4H, **53**, H1/H2); 3.47-3.52 (m, **41**, H2, **53**, H3); 3.59 (dd, J₁ = 6.5 Hz, J₂ = 7.1 Hz, 2H, **41**, H3); 3.64 (dd, J₁ = 4.5 Hz, J₂ = 7.3 Hz, H4, **53**) 3.74 (s, 3H, **41**, -OMe); 3.78 (s, 3H, **53**, -OMe) 4.28 (dd, J₁ = 9.5 Hz, J₂ = 7.1 Hz), 2H, **41**, H4); 6.55-6.61 (m, 2H, **41**, H5); 6.74-6.82 (m, 2H, **41**, H6); 6.84-6.88 (m, 2H, **53**, H5); 7.37-7.42 (m, 2H, **53**, H6)

Fraction 5 (crude **54**):

¹H NMR (500 MHz, CDCl₃): δ = 2.48-2.51 (m, NH); 2.62 (t, 4H, H1); 3.12 (t, 4H, H2); 3.58-3.68 (m, NH); 3.75 (s, 6H, H3); 6.60 (d, 2H, H4); 6.79 (d, 2H, H5).

7.6.1.2 Solution and solid phase experiments (table 19)

Synthesis of **42** via the ethyl carbamate **55**

Bis(chloroethyl)amine, hydrochloride (0.25 g, 1.4 mmol, 1 equiv) was dissolved in water (5 mL). Ethyl chloroformate (0.18 g, 1.7 mmol, 1.2 equiv) and potassium carbonate (0.40 g, 2.8 mmol, 2 equiv) was added and the solution was stirred at room temperature for 2.5 h. 4-methoxyaniline (0.88 g, 7 mmol, 5 equiv), potassium carbonate (0.48 g, 3.5 mmol, 2.5 equiv) and potassium iodide (0.23 g, 1.4 mmol, 1 equiv) was added, the vessel was sealed and heated with microwaves (120 °C, 40 min). The solution was extracted with toluene (6 x 10 mL) and combined organic phases were washed with saturated aqueous sodium bicarbonate (10 mL) and water (10 mL), dried (anhydrous sodium sulphate) and evaporated. The residue was purified through automated flash chromatography (ethyl acetate/heptane) to give 20 mg (4 %) of **42**, 50 mg of (4-methoxyphenyl) carbamic acid ethyl ester **59** (15 %) and trace amount of **41**. No piperazine **57** was found.

¹H NMR of **59** (500 MHz, CDCl₃): δ = 1.23 (t, 3H, H1); 3.11 (q, 3H, H2); 3.74 (a, 3H, H3); 6.58 (d, 2H, H4); 6.78 (d, 2H, H5).

Synthesis of **42** via the 2-methoxyethyl carbamate of the mustard (**56**)

Bis(chloroethyl)amine, hydrochloride (0.25 g, 1.4 mmol, 1 equiv) was dissolved in water (5 mL). 2-Methoxyethyl chloroformate (0.23 g, 1.7 mmol, 1.2 equiv) and potassium carbonate (0.43 g, 2.8 mmol, 2 equiv) was added and the solution was stirred at room temperature for 3.5 h. 4-methoxyaniline (0.86 g, 7 mmol, 5 equiv),

potassium carbonate (0.48 g, 3.5 mmol, 2.5 equiv) and potassium iodide (0.23 g, 1.4 mmol, 1 equiv) was added, the vessel was sealed and heated with microwaves (120 °C, 40 min). The solution was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with saturated aqueous sodium bicarbonate (10 mL) and water (10 mL), dried (anhydrous sodium sulphate) and evaporated. The residue was purified through automated flash chromatography (ethyl acetate/heptane) to yield 46 mg (10 %) of compound **42** and 45 mg of compound **58** (11 %)

¹H NMR of **58** (500 MHz, CDCl₃): δ = 3.00-3.04 (m, 4H, H1); 3.40 (s, 3H, H2); 3.60 (t, 2H, H3); 3.63-3.66 (m, 4H, H4); 3.77 (s, 3H, H5); 4.26 (t, 2H, H6); 6.83-6.92 (m, 4H, H7).

Resin **31** (1.0 g, 1.4 mmol, 1 equiv) was suspended in water (5 mL). 4-methoxyaniline (0.87 g, 7 mmol, 5 equiv), potassium carbonate (0.48 g, 3.5 mmol, 2.5 equiv) and potassium iodide (0.23 g, 1.4 mmol, 1 equiv) was added, the vessel was sealed and heated with microwaves (120 °C, 40 min). The suspension was filtered and the resin was washed with THF (2 x 20 mL); ethanol (2 x 20 mL); water (2 x 20 mL); ethanol (2 x 20 mL); THF (20 mL) and ethanol (20 mL). The filtrate was washed with ethyl acetate (25 mL) made strongly basic with aqueous ammonia (25 % v/w; 25 mL) and extracted again with ethyl acetate (2 x 50 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (10 mL) and water (10 mL), dried (anhydrous sodium sulphate) and evaporated. Purification through automated Flash Chromatography (ethyl acetate/heptane) to yield 100 mg (20 %) of **42**

¹H NMR (500 MHz, CDCl₃): δ = 3.29 (t, J = 6.1 Hz, 2H, H1); 3.49 (dd, (J₁ = 6.3 Hz, J₂ = 8.5 Hz), 2H, H2); 3.54 (t, J = 6.0 Hz, 2H, H3); 3.73 (s, 3H, H4); 3.75 (dd, (J₁ = 7.6 Hz, J₂ = 9.6 Hz) 2H, H5); 3.79 (s, 3H, H6); 6.60 (d, J = 9 Hz, 2H, H7); 6.77 (d, J = 8.9 Hz, 2H, H8); 6.88 (d, J = 9.1 Hz, 2H, H9); 7.43 (d, J = 9.1 Hz, 2H, H10) (Appendix A - spectrum 7)

¹³C NMR (125 MHz, CDCl₃): δ = 159.2 (C1); 155.8 (C2); 152.6 (C3); 142.7 (C4); 134.2 (C5); 119.9 (C6); 115.4 (C7); 114.5 (C8); 114.4 (C9); 56.2 (C10); 55.9 (C11); 44.5 (C12); 43.8 (C13); 43.5 (C14); 42.9 (C15). (Appendix A - spectrum 8)

Anal calc for C₁₉H₂₂N₃O₃: C, 66.84 H, 6.79 N, 12.31 Found C, 67.00 H, 7.08 N, 11.64

7.6.2 Resin microwave screening experiments (table 20)

Resin (1.0 g, 1.5 mmol, 1 equiv) was suspended in 5 mL water with 4-methoxyaniline (0.91 g, 7.4 mmol, 5 equiv), potassium carbonate (0.51 g, 3.7 mmol, 2.5 equiv) and potassium iodide (1.2 g, 1.5 mmol, 1 equiv) in a 20 mL vessel. The vessel was sealed and the reaction was heated with microwaves (120 °C, 40 min). The suspension was filtered and the resin was washed with water (2 x 10 mL), THF (2 x 10 mL), ethanol (2 x 10 mL), water (2 x 10 mL), THF (2 x 10 mL) and ethanol (2 x 10 mL) and then dried. The organic solvent was evaporated from the filtrate and the water phase was extracted with toluene (3 x 20 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (10 mL) and water (10 mL) and evaporated.

The residue was purified through automated flash chromatography (ethyl acetate/heptane).

All residues gave satisfactory ^1H NMR spectra and LC/MS for **42**.

7.6.3 NMR experiments

Addition of 4-methoxyaniline to **31** followed by ^{13}C NMR

Resin **31** (3.6 g; 5.0 mmol; 1 equiv) was suspended in 35 mL water with 4-methoxyaniline (3.07 g; 25 mmol; 5 equiv), potassium carbonate (1.75 g; 12.5 mmol; 2.5 equiv) and potassium iodide (1.66 g; 10 mmol; 2 equiv) and heated to 80°C. Samples of resin were removed at regular intervals, washed with deuterated water in an NMR tube and cooled to 5 degrees. ^{13}C gel-phase NMR was taken, first in deuterated water, then in deuterated chloroform.

Addition of iodide to **31** in situ in an NMR tube (table 21)

Resin **31** (0.2 g, 0.3 mmol, 1 equiv) was suspended in 1 mL deuterated water in an NMR tube. Potassium iodide (50 mg, 0.3 mmol, 1 equiv) was added and the reaction was placed in the spectrophotometer and heated to 80°C. ^{13}C NMR was recorded every half hour (scans) (Appendix spectrum 9 and 10)

7.6.4 Parallel experiments at 60 °C, 80 °C and 100 °C

General procedure for parallel experiments (Table 22, 23 and 24)

Resin **31** (1.0 g, 1.4 mmol, 1 equiv) was suspended in water (10 mL) with 4-methoxyaniline (0.86 g, 7 mmol; 5 equiv) and the amounts of base and potassium iodide stated in the tables: K_2CO_3 (0.48 g, 3.5 mmol, 2.5 equiv OR 0.24 g, 1.75 mmol, 1.25 equiv OR none) and KI (0.46 g, 2.8 mmol, 2 equiv OR 0.23 g, 1.4 mmol, 1 equiv OR none)

The suspensions were heated to the stated temperature and shaken at the stated time. The suspensions were filtered and the resin was washed with THF (2 x 20 mL); ethanol (2 x 20 mL), water (2 x 20 mL); THF (2 x 20 mL) and ethanol (2 x 20 mL) and then dried. The filtrates were concentrated to approximately 60 mL, aqueous ammonia (25% w/v; 10 mL) was added and the filtrates were extracted with toluene (4 x 20 mL). The combined organic phases were washed with saturated sodium bicarbonate (10 mL) and water (10 mL), dried (anhydrous sodium sulphate) and evaporated. Brown residue was purified using FlashMaster (ethyl acetate/heptane).

Main products from all residues gave satisfactory ^1H NMR and LC/MS for **42**

The slower running hydrolysis products **41** and **53** were isolated in trace amounts and identified from their ^1H NMR spectra. Examples of spectra:

53 (from table 25, entry 3 – appendix A spectrum 11)

^1H NMR (500 MHz, CDCl_3): δ = 3.40-3.46 (m, 4H, H1/H2); 3.51 (t, J = 6.5 Hz, 2H, H3); 3.65 (dd, J_1 = 7.3 Hz, J_2 = 9.9 Hz, 2H, H4); 3.78 (s, 3H, H5, (OMe)); 6.88 (d, J = 8.9 Hz, 2H, H6); 7.40 (d, J = 8.9 Hz, 2H, H7)

41 (from table 25, entry 3 – appendix A spectrum 12)

^1H NMR (500 MHz, CDCl_3): δ = 3.32 (t, J = 6.1 Hz, 2H, H1); 3.52 (t, J = 6.1 Hz, 2H, H2); 3.60 (dd, J_1 = 6.8 Hz, J_2 = 9.3 Hz, 2H, H3); 3.74 (s, 3H, H4 (OMe)); 4.30 (dd, J_1 = 7.6 Hz, J_2 = 9.2 Hz, 2H, H5), 6.60 (d, J = 8.9 Hz, 2H, H6); 6.89 (d, J = 8.9 Hz, H7).

7.7 Immobilized Metalloporphyrins as catalysts

7.7.1 Porphyrin synthesis

7.7.1.1 Synthesis of 5-(4-hydroxy)-10,15,20-tetraphenylporphyrin (66)

5-(4-methoxy)-10,15,20-tetraphenylporphyrin (62)

4-methoxybenzaldehyde (9.2 mL (10 g, 80 mmol, 1 equiv) and benzaldehyde (23 mL, 24 g, 220 mmol, 3 equiv) were added to propionic acid at reflux (550 mL) in atmosphere. Distilled pyrrole (21 mL, 22 g, 330 mmol, 4 equiv) was added, the mixture turned black and was kept at reflux for 3 h open to the atmosphere.

The solution was cooled down and the porphyrins precipitated over the following days as purple crystals. Extensive column chromatography (40-60 petroleum ether/dichloromethane) yielded 1.07 g (2 %) of the desired porphyrin.

^1H -NMR: (400 MHz, CDCl_3): (-)2.75 – (-) 2.73 (m, 2H, NH); 4.10 (s, 3H, -OMe); 7.30 (d, J = 8.6 Hz, 2H, H1); 7.73-7.83 (m, 9H, H2); 8.13 (d, J = 8.5 Hz, 2H, H3); 8.20-8.24 (m, 6H, H4); 8.82-8.89 (m, 8H, H5).

5-(4-hydroxy)-10,15,20-tetraphenylporphyrin (66)

62 (650 mg, 1 mmol, 1 equiv) was dissolved in freshly distilled dichloromethane (30 mL) under Ar. The solution was cooled to -78°C and BBr_3 (3 mL, 1.1 g, 4.5 mmol, 4.5 equiv) was added quickly. The cooling was removed and the reaction was stirred at room temperature overnight. Reaction was quenched by addition of methanol at -78°C and made basic with 20 mL triethyl amine. The solution are diluted with 200 mL ethyl acetate and washed with 100 mL Sodium bicarbonate (sat) and 2x 100 mL water. The organic phase was dried (anhydrous sodium sulphate) and evaporated.

Column chromatography (dichloromethane) yielded 760 mg (73%) of **66**.
Overall yield (1.5 %)

¹H-NMR (400 MHz, CDCl₃): δ = (-)2.86 – (-)2.59 (m, 2H, NH); 7.19 (d, J = 8.3 Hz, 4H, H1); 7.71-7.78 (9H, m, H2); 8.07 (d, J = 8.3 Hz, 2H, H3); 8.20-8.25 (m, 6H, H4); 8.81-8.90 (m, 8H, H5).

5-(4-hydroxy)-10,15,20-tetraphenylporphyrin (66) by deprotection of crude porphyrin mixture

4-methoxybenzaldehyde (9.5 mL (ρ = 1.123 g/mL), 10.7 g, 78 mmol, 1 equiv) and benzaldehyde (22.5 mL (ρ = 1.04 g/mL), 23.4 g, 221 mmol, 3 equiv) were added to propionic acid (500 mL) at reflux temperature. Distilled pyrrole (20.5 mL (ρ = 0.969 g/mL), 19.9 g, 297 mmol, 4 equiv) was added and the solution was kept at reflux temperature for 1.5 h, then placed in a freezer for 5 days. The precipitated porphyrins were removed by filtration.

Yield: 1.87 g

The product was deprotected in two batches.

Representative procedure:

Crystals (900 mg, 1.39 mmol, 1 equiv) were dissolved in dichloromethane (30 mL) under Ar. The solution was cooled to -78°C and boron tribromide (2.6 mL, (ρ = 2.65 g/mL), 6.9 g, 28 mmol, 20 equiv) was added quickly and the cooling was removed. After 3 h the reaction was cooled again to -78°C and the reaction was quenched with methanol (20 mL), made basic with triethyl amine (10 mL), then allowed to warm to room temperature. Another batch (948 mg) was deprotected in the same way. The combined batches were evaporated and the residue dissolved in dichloromethane (70 mL), which was washed with water (30 mL), dried (anhydrous sodium sulphate) and evaporated. The residue was purified by column chromatography (Eluent (40-60 petroleum ether/ethyl acetate)

Yield of **66** (both batches 640 mg (1.3 %).

¹H-NMR (400 MHz, CDCl₃): δ = (-) 2.80 – (-) 2.71 (NH); 7.21 (d, J = 8.4 Hz, 2H, H1); 7.72-7.79 (m, 9H, H2); 8.08 (d, J = 8.3 Hz, 2H, H3); 8.19-8.25 (m, 6H, H4); 8.81-8.90 (m, 8H, H5)

7.7.1.2 Synthesis and metallation of porphyrin complexes 69 and 70.

Initial synthesis of resin-bound porphyrin 67

Resin (0.30 g, 0.45 mmol, 1 equiv) was suspended in freshly distilled dichloromethane (2 mL) under Ar and cooled on an ice bath. Mesyl chloride (0.7 mL (ρ =1.48 g/mL), 1.03 g, 9 mmol, 20 equiv) was added followed by pyridine (0.25 mL (ρ =0.935 g/mL), 0.27 g, 38 mmol, 84 equiv). The ice bath was removed and the suspension was stirred for 1.5 h at room temperature. The solvent was removed and the reaction was repeated.

The suspension was filtered and the resin was washed with DCM (3 x 10 mL) and DMF (3 x 10 mL). The resin was suspended in a solution of **66** (370 mg, 0.59 mmol;

1.3 equiv) and sodium hydroxide (19 mg; 0.48 mmol; 1.1 equiv) in DMF (8 mL) at 90 °C. The suspension was stirred overnight, then cooled down and filtered. The red resin was washed with DMF (3 x 10 mL), DCM (3 x 10 mL), acetone (3 x 10 mL), water (3 x 10 mL), methanol (3 x 10 mL) and DCM (3 x 10 mL), then dried

End weight 198 mg (70% of theoretical gain)

Elemental analysis: 3.54% N (71 % of theoretical gain from 0.4 % in starting material)

IR showed new peaks at 1735 cm⁻¹; 1606 cm⁻¹; 1559 cm⁻¹

1508 cm⁻¹, 1175 cm⁻¹ (aromatic) 3320 cm⁻¹ (NH)

Example of synthesis of resin-bound catalyst 69

Versabeads (0.60 g, 0.9 mmol, 1 equiv) was suspended in freshly distilled dichloromethane (5 mL) on ice. Mesyl chloride (1.5 mL (ρ =1.48 g/mL), 2.2 g, 19 mmol, 21 equiv) was added followed by pyridine (1.0 mL (ρ =0.935 g/mL), 0.94 g, 12 mmol, 13 equiv). The suspension was stirred for 1 h at room temperature, then the solvent was removed and the reaction repeated to give resin **28**. **66** (900 mg; 1.4 mmol; 1.6 equiv) were dissolved in DMF (15 mL). Sodium hydroxide (43 mg, 1.1 mmol, 1.2 equiv) was added and the solution was heated to 90°C for 2 h. The mesylated resin **28** was added and the suspension was stirred at 90°C for 20 h. The suspension was filtered, and the resin was washed with DMF (3x10 mL), DCM (3 x 10 mL), acetone (3 x 10 mL), water (3 x 10 mL), Methanol (3 x 10 mL) and DCM (3 x 10 mL), then dried

End weight 682 mg of **68**

557 mg of the resin was suspended in DMF (10 mL) under Ar. MnCl₂*4H₂O (8.3 g, 42 mmol, > 100 equiv) was added and the suspension was heated under Ar and kept at reflux for 3 h. the suspension was filtered and the resin washed with water (3 x 10 mL), acetone (3 x 10 mL), DCM (3 x 10 mL), methanol (3 x 10 mL).

End weight: 562 mg

NH stretch at 3320 cm⁻¹ was gone.

Mn- loading by AAS: 0.2 mmol Mn/g ~ 50% of theory (overall from Versabeads).

Example of immobilization of 5,10,15,20-tetra(pentafluorophenyl)porphyrin on solid phase to form complex 68 and metallation to form 70

Versabeads A800 (286 mg, 1 mmol, 1 equiv) was suspended in DMF (4 mL) with 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (140 mg, 0.14 mmol, 1.4 equiv) in an Emrys Process Vial. DIPEA (20 μ L (ρ =0.79 g/mL), 18 mg, 0.14 mmol, 1.4 equiv) was added, the reaction vessel was sealed and the suspension was heated to 110°C overnight. The suspension was filtered and the resin was washed with DCM and diethyl ether alternating (5 mL) until no visible colour was detected in the washing solution.

End weight: 318 mg

¹⁹F gel-phase NMR (400 MHz; CDCl₃): -136 ppm; -141 ppm; -152 ppm; -160 ppm; -162 ppm. (TPFPP: -136; -151; -161) (Appendix A – spectrum 13)

FTIR: New peaks at 1500 cm⁻¹ 988 cm⁻¹ and 759 cm⁻¹ (aryl peaks)

68 (122 mg) were suspended in DMF (3 mL) with MnCl₂*4H₂O (0.6 g; >100 equiv) and the suspension was heated at reflux temperature for 2 h. The suspension was

filtered and the resin was washed with water (3 x 10 mL), acetone (3 x 10 mL) and DCM (3 x 10 mL), then dried.

AAS Mn Content: 78 $\mu\text{mol/g}$ (12 % overall yield from PEGA resin)

FTIR: Peak at 1500 cm^{-1} gone, new peak at 945 cm^{-1} compared to **68**.

7.7.2 Test reactions

Oxidation of thioanisole with *tert*-butyl hydroperoxide (Table 28 and 29)

Sulfide oxidations were performed at room temperature. Thioanisole and 1,2 – dichlorobenzene (internal standard) were added as a standard solution in acetonitrile. Imidazole and catalyst or other additives were added neat to the solution. *Tert*-butyl hydroperoxide was added as a commercially available 70% (w/w) solution in water. Reactions were performed under Ar and monitored by GC measurements of the substrate peak relative to the internal standard.

Sodium periodate epoxidation

70 (19 mg, 1.5 μmol , 1 equiv) was placed in an Irori Kan™ and added to a solution of styrene (12 mg, 0.11 mmol, 73 equiv), imidazole (4 mg, 57 μmol , 39 equiv) and 1,2 – dichlorobenzene (4 μL) in 2 mL acetonitrile. Sodium periodate (49 mg, 0.23 mmol, 153 equiv) was added as a solution in water (1 mL) and the mixture was stirred at room temperature and monitored by GC.

| Time | Conversion | Comment |
|------|------------|------------------|
| 12 h | 54% | Catalyst removed |
| 24 h | 84% | |

Catalyst was washed with acetonitrile (3 x 10 mL); water (3 x 10 mL); acetonitrile (3 x 10 mL) and dichloromethane (3 x 10 mL), then reused.

Reuse of catalyst under the same conditions gave 14% conversion after 12h.

7.7.3 Attempted synthesis of porphyrins directly on solid-phase

Synthesis of meso-phenyldipyrromethane **71**

Benzaldehyde (0.30 mL ($\rho=1.044\text{ g/mL}$), 0.32 g, 3 mmol, 1 equiv) was added to distilled pyrrole (15 mL) at room temperature. Trifluoroacetic acid (20 μL) was added and the solution was stirred for 50 min, then diluted with dichloromethane. The organic phase was washed with aqueous NaOH solution (2 %, 2 x 40 mL) and water (2 x 50 mL), dried (anhydrous sodium sulphate) and evaporated. Column chromatography (diethyl ether/40-60 petroleum ether) yielded 350 mg of meso-phenyldipyrromethane **71** (53%) as yellow oil.

^1H – NMR (400 MHz, CDCl_3): δ = 2.17 (acetone impurity) 5.48 (s, 1H, H1) 5.91-5.94 (m, 2H, H2) 6.14-6.17 (m, 2H, H3) 6.68-6.71 (m, 2H, H4) 7.19-7.35 (m, 5H, phenyl-) 7.92 (br s, 2H, NH)

^{13}C – NMR (100 MHz, CDCl_3) δ = 142.1 (C1) 132.5 (C2) 128.6 (C3) 128.4 (C4) 127.0 (C5) 117.2 (C6) 108.5 (C7) 107.2 (C8) 44.0 (C9) 30.9 (acetone impurity)

Attempted synthesis of porphyrin on resin

With boron trifluoride diethyletherate:

Versabeads O400 (1.3 g, 2.0 mmol, 1 equiv) was suspended in freshly distilled dichloromethane (8 mL) under Ar. The suspension was cooled down on ice/water bath. Mesyl chloride (3.0 mL (ρ =1.48 g/mL), 4.47g, 39 mmol, 20 equiv) was added followed by pyridine (1 mL (ρ =0.935 g/mL), 0.94 g, 12 mmol, 6 equiv) and the reaction proceeded at room temperature for 1 h. The reaction was repeated under the same conditions, and the resin was filtered and washed (6x10 mL DCM).

IR = 1174 cm^{-1} (SO stretch)

4-hydroxybenzaldehyde (1.26 g, 10.3 mmol, 5.8 equiv) and sodium hydroxide (0.39 g, 9.75 mmol, 5 equiv) were suspended in DMF (20 mL) and heated to 90 °C. The mesylated resin was added and the suspension was kept at 90°C overnight.

The suspension was filtered and the resin was washed with DCM (3 x 10 mL), acetonitrile (3 x 10 mL), water (3 x 10 mL), methanol (3 x 10 mL) and DCM (3 x 10 mL) then dried to give resin **26**.

IR: 1689 cm^{-1} ; 1600 cm^{-1} ; 1578 cm^{-1} ; 1509 cm^{-1} ; 834 cm^{-1} (Corresponds to IR of 4-hydroxybenzaldehyde)

Resin (250 mg, 0.33 mmol, 1 equiv) was carefully dried and placed in a flask with **26** (215 mg; 0.975 mmol; 3 equiv). The flask was evacuated and filled with argon three times. Freshly distilled dichloromethane was added and the suspension was degassed 3 times. Benzaldehyde (0.05 mL; (ρ =1.044 g/mL) 52 mg; 0.49 mmol; 1.5 equiv) was added followed after 20 minutes by $\text{BF}_3 \cdot \text{OEt}_2$ (0.05 mL (ρ =1.154 g/mL) 58 mg; 0.41 mmol; 1.2 equiv). The flask was covered with foil and allowed to stand for 2 h. Resin was then filtered and washed with alternating acetone and dichloromethane until no colour remained in washing, then dried.

End weight: 287 mg

IR revealed none of the characteristic bands from porphyrin.

With trifluoroacetic acid:

Resin **26** (0.3 g, 0.4 mmol, 1 equiv) was suspended in freshly distilled dichloromethane (10 mL) with **71** (0.24 g, 1.1 mmol, 2.8 equiv) at room temperature under Ar. Benzaldehyde (0.11 mL (ρ = 1.04 g/mL), 1.1 mmol, 2.8 equiv) was added and the suspension was stirred for 1 h. Trifluoroacetic acid (0.03 mL (ρ = 1.98 g/mL), 45 mg, 0.4 mmol, 1 equiv) was added and the suspension turned red. The suspension was stirred for 2 h, then DDQ (575 mg, 2.5 mmol, 6.3 equiv) was added and the suspension turned black. The suspension was heated at reflux for 1 h, the filtered and the black beads were washed with DCM (5 mL), DMF (5 mL), acetone (5 mL), DMF (2 x 5 mL), acetone (5 mL), methanol (5 mL) and DCM and then dried.

IR showed no change from Versabeads O

With propionic acid:

Resin **26** (250 mg; 0.33 mmol; 1 equiv) was suspended in propionic acid (5 mL) and the suspension was heated to reflux. Benzaldehyde (0.1 mL ($\rho=1.044$ g/mL), 104 mg, 0.98 mmol, 3 equiv) was added, followed by freshly distilled pyrrole (0.09 mL ($\rho=0.969$ g/mL), 87 mg, 1.3 mmol, 4 equiv). The suspension was kept at reflux for 3 h, then filtered and washed with alternating acetone and DCM (5 mL) until the washing was colourless, then dried.

End weight 295 mg

IR contained possible porphyrin peaks (1735 cm^{-1} ; 1606 cm^{-1} ; 1175 cm^{-1}) but the spectrum looked blurred.

7.7.4 Attempted synthesis of a lanthanide porphyrin complex

Resin **67** (77 mg, 0.06 mmol, 1 equiv) was suspended in DMF (5 mL). The suspension was heated to reflux, and Ytterbium(III) chloride, hexahydrate (2.0 g, 5.1 mmol, 85 equiv) was added and the suspension was kept at reflux temperature for 3.5 h. The resin was filtered, washed with DMF (3 x 5 mL), THF (3 x 5 mL), water (3 x 5 mL) and DCM (3 x 5 mL) and then dried.

IR still showed NH proton stretch: 3315 cm^{-1} .

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9 Appendix

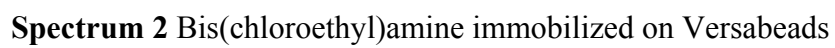
Appendix A – Selected NMR spectra

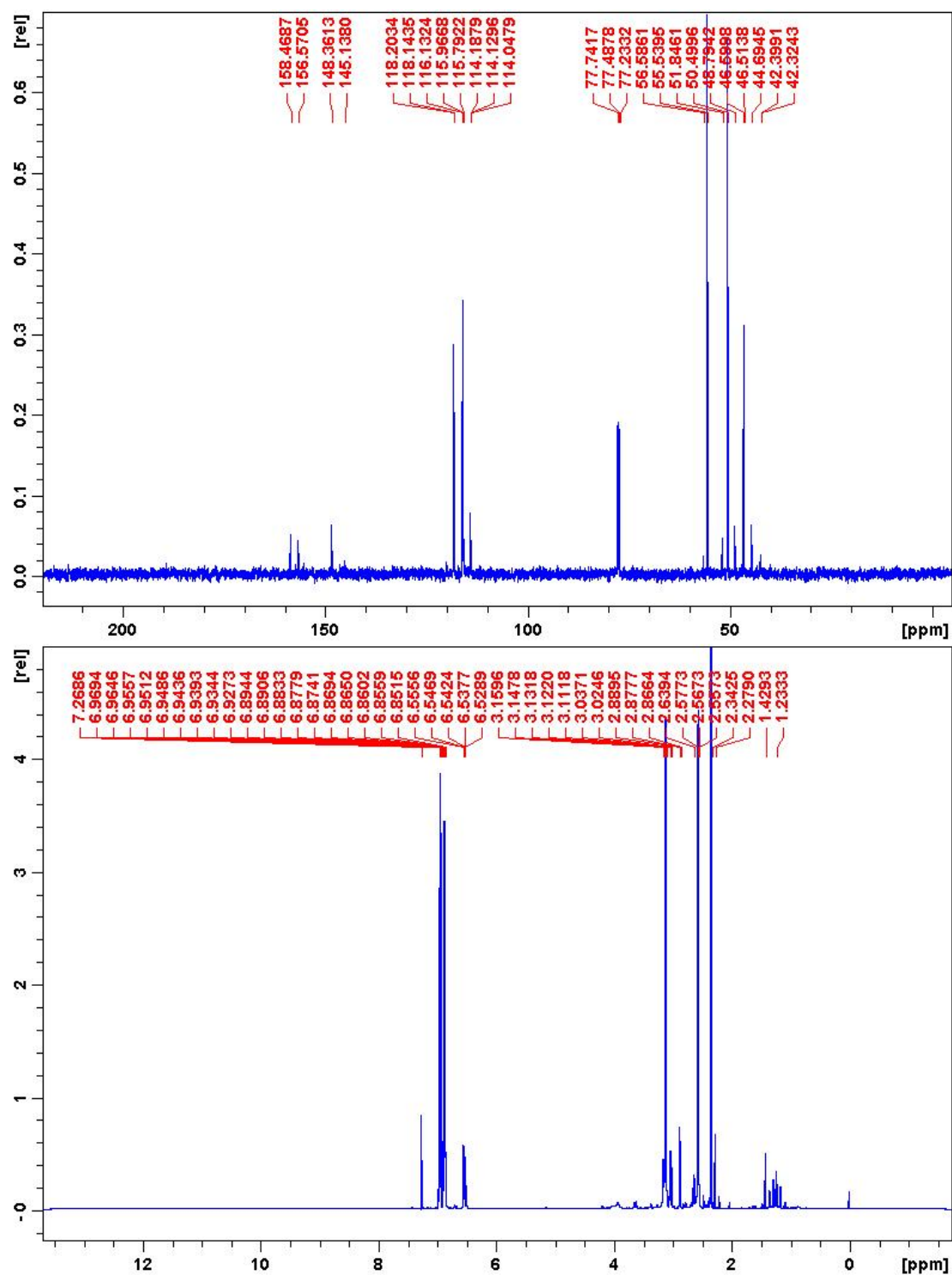
Appendix B – Publications

APPENDIX A

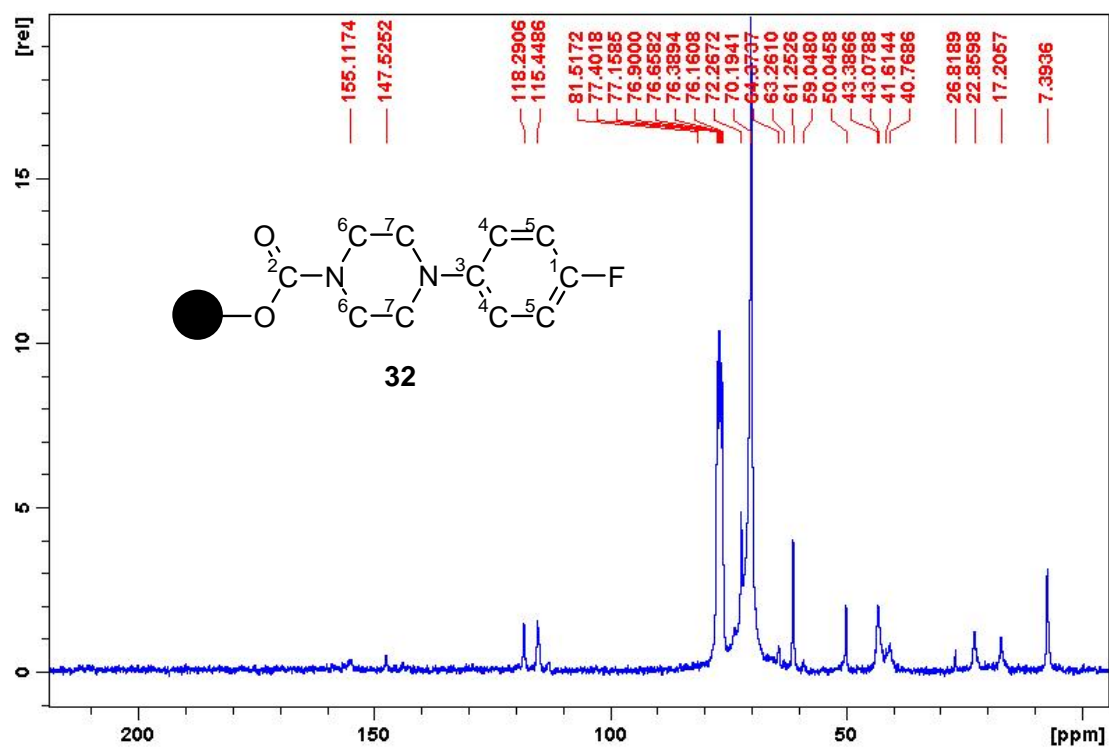
Selected NMR spectra

| | |
|--------------------|------------------------------------------------------------------------------------------------------------------------|
| Spectrum 1: | ^{13}C gel-phase NMR of VersabeadsO400 |
| Spectrum 2: | Bis(chloroethyl)amine immobilized on Versabeads (31) |
| Spectrum 3 and 4: | ^1H and ^{13}C NMR of product from the reductive cleavage of resin 32 from Table 13, entry 2. |
| Spectrum 5: | ^{13}C gel-phase NMR spectrum of resin 32 |
| Spectrum 6: | Example of ^{13}C gel-phase NMR reaction monitoring |
| Spectrum 7: | ^1H NMR of the imidazolidin-2-one 42 |
| Spectrum 8: | ^{13}C DEPT NMR of the imidazolidin-2-one 42 |
| Spectrum 9 and 10: | The reaction between resin 31 and KI in an NMR tube |
| Spectrum 11: | Hydrolysis product 53 |
| Spectrum 12: | Hydrolysis product 41 |
| Spectrum 13: | ^{19}F NMR of resin 68 compared to starting material |

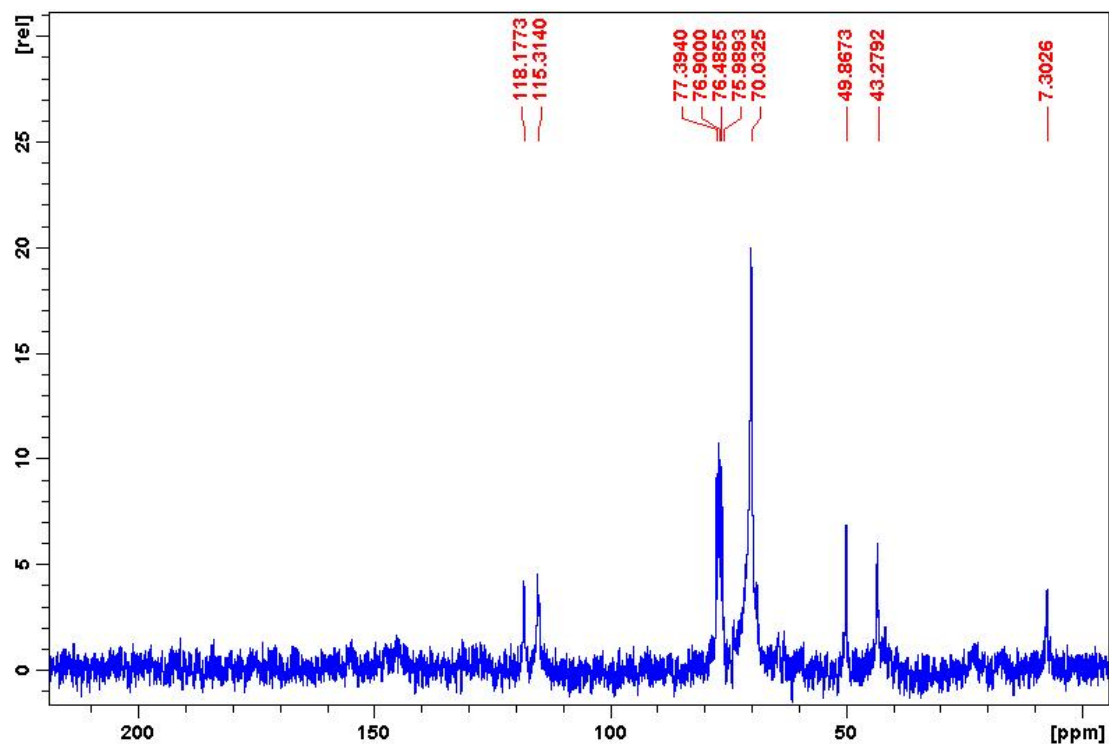




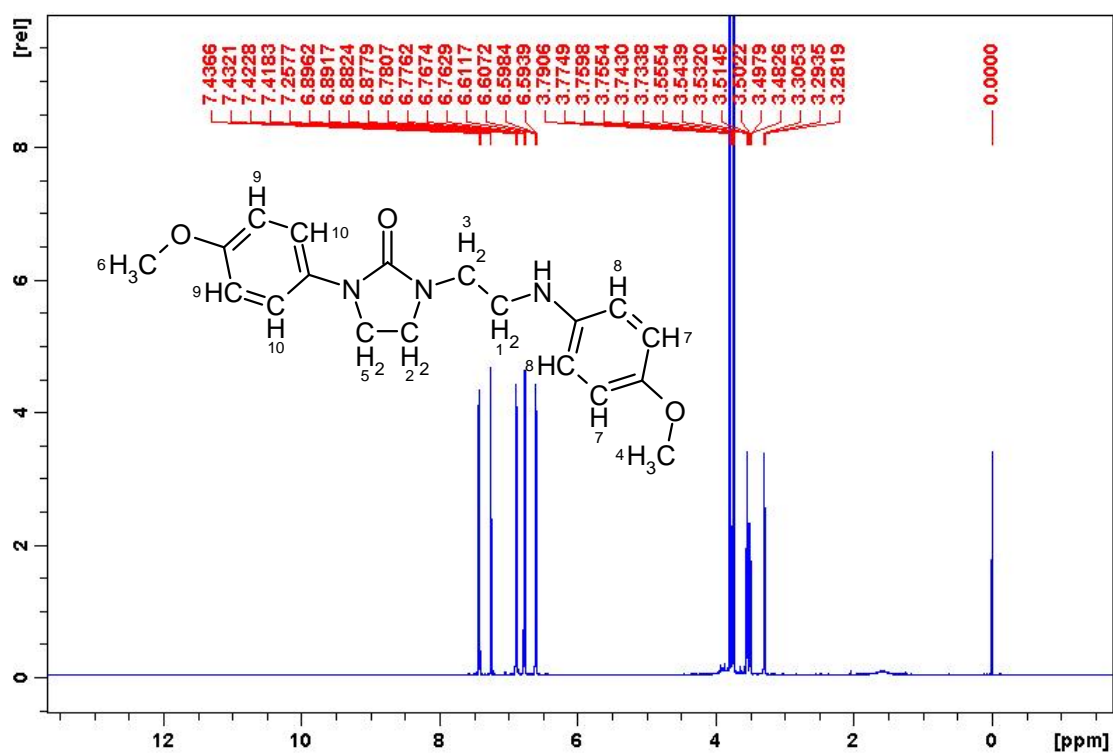
Spectrum 3 and 4 ^1H and ^{13}C NMR of product from the reductive cleavage of resin **32** from Table 13, entry 2. The peaks at 2.88 ppm and 3.12 ppm (obscured by piperazine peak) correlates to the ^{13}C NMR peaks at 44.7 ppm and 48.8 ppm in the HSQC, which is in accordance with literature results for similar triamines.



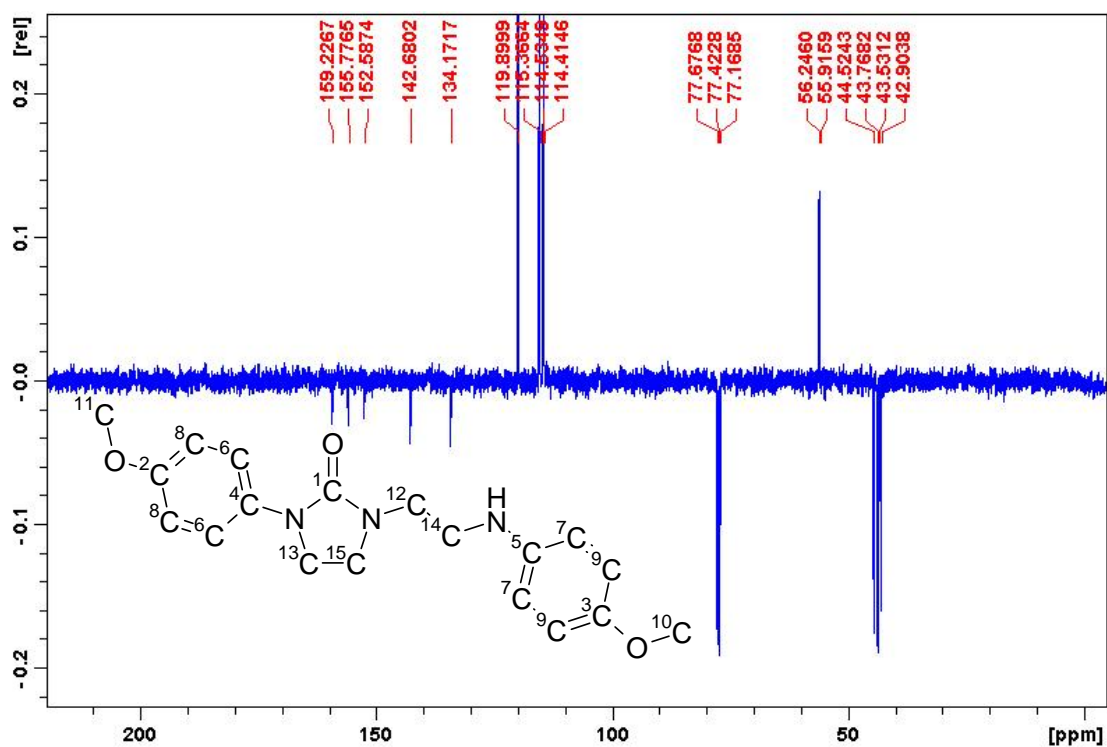
Spectrum 5 ^{13}C gel-phase NMR spectrum of resin **32** from Table 13, entry 6. Cleavage extent is estimated from the height of the peaks at 64.4 ppm ($-\text{CH}_2\text{CH}_2\text{OR}$) and 61.3 ppm ($-\text{CH}_2\text{CH}_2\text{OH}$).



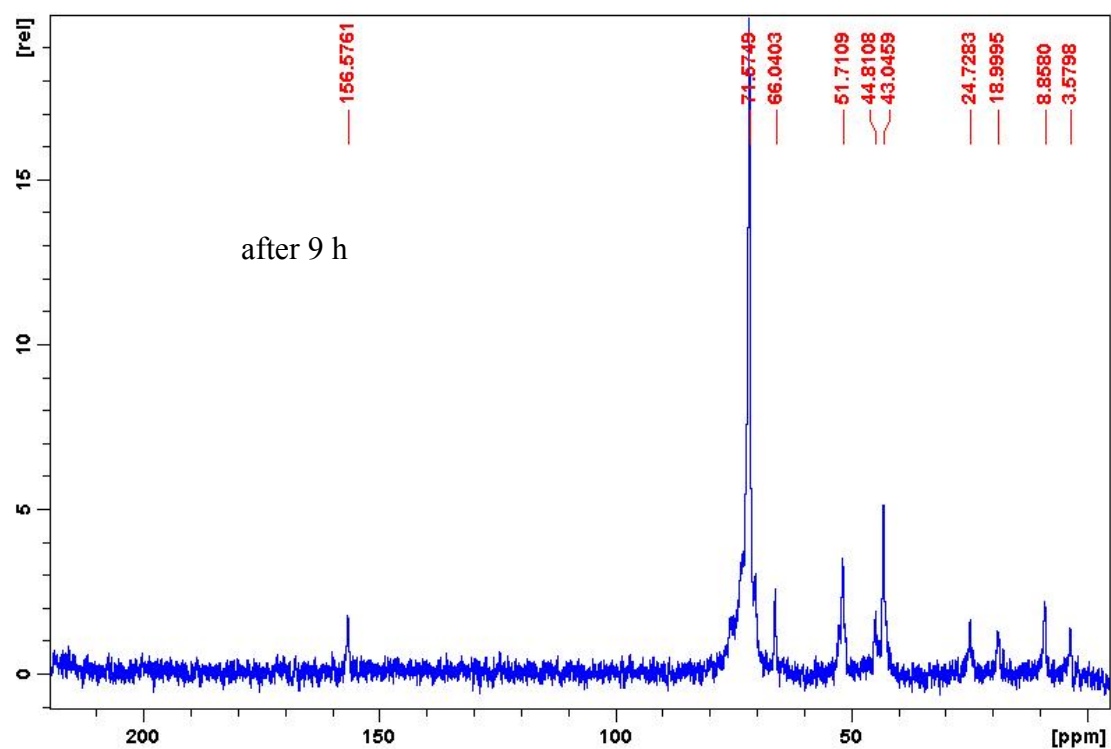
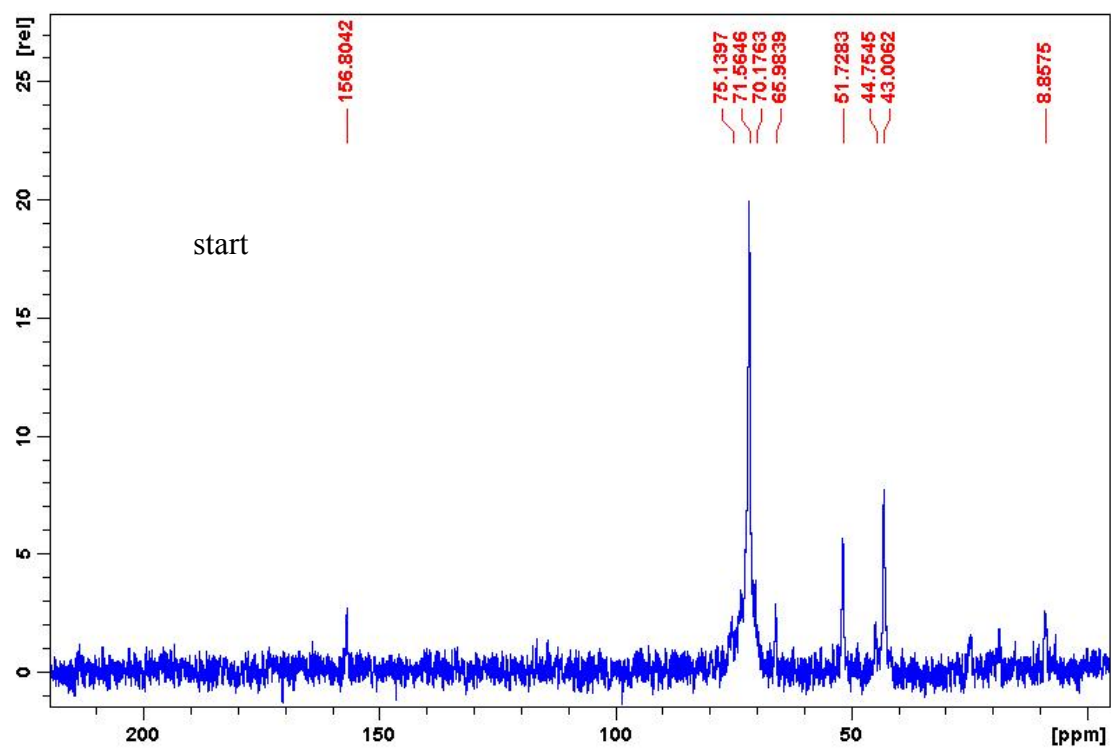
Spectrum 6 Example of reaction monitoring using ^{13}C gel-phase NMR: A sample from the reaction of 4-fluoroaniline with resin **31** (1024 scans). Note that the peak at 41 ppm ($-\text{NCH}_2\text{CH}_2\text{Cl}$) (**31**) has been replaced by a peak at 43 ppm ($-\text{NCH}_2\text{CH}_2\text{N}$) (**32**).



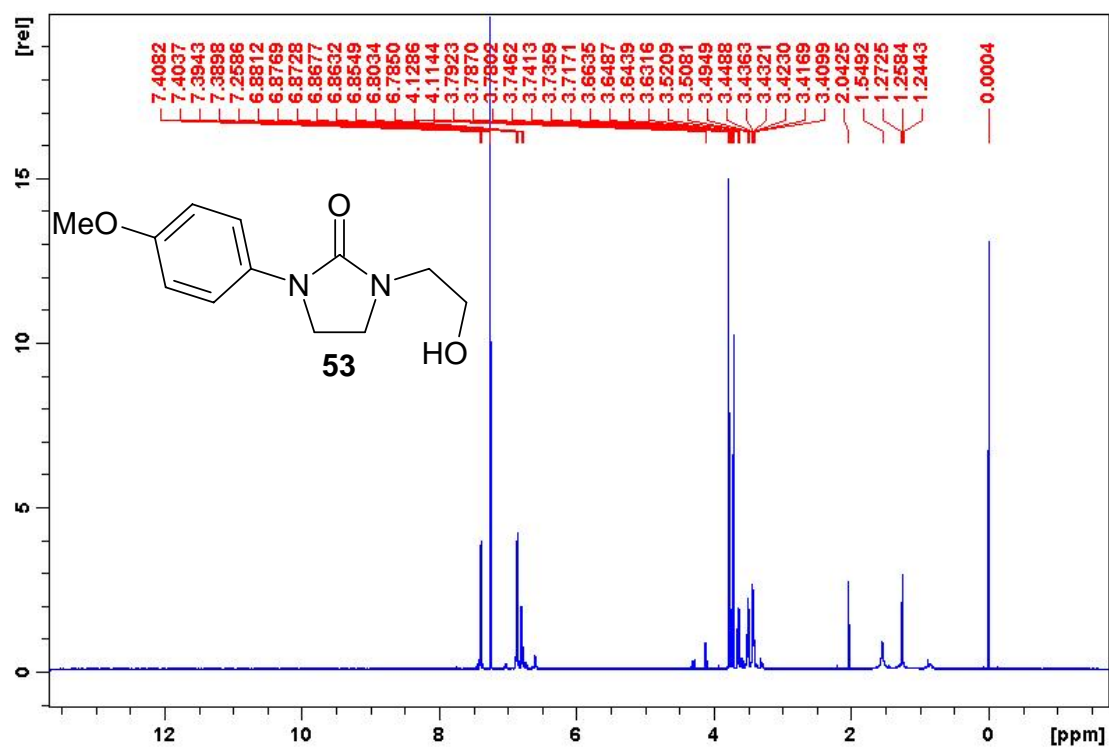
Spectrum 7: ^1H NMR of the imidazolidin-2-one **42**.



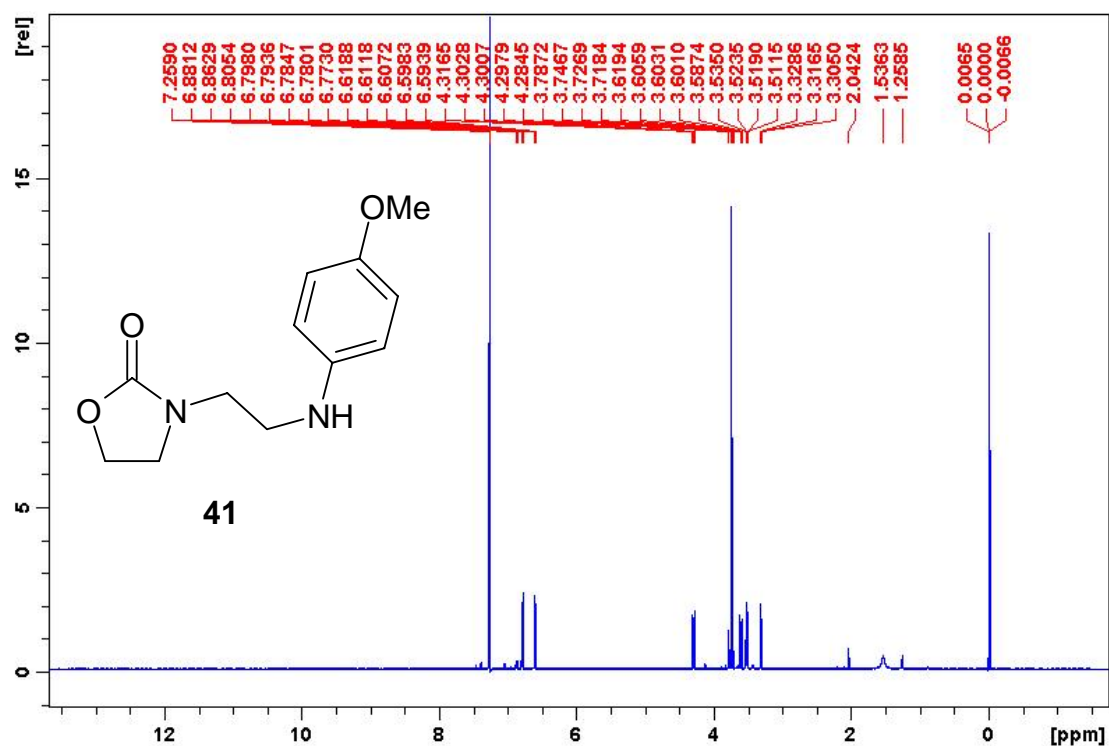
Spectrum 8: ^{13}C DEPT NMR of the imidazolidin-2-one **42**



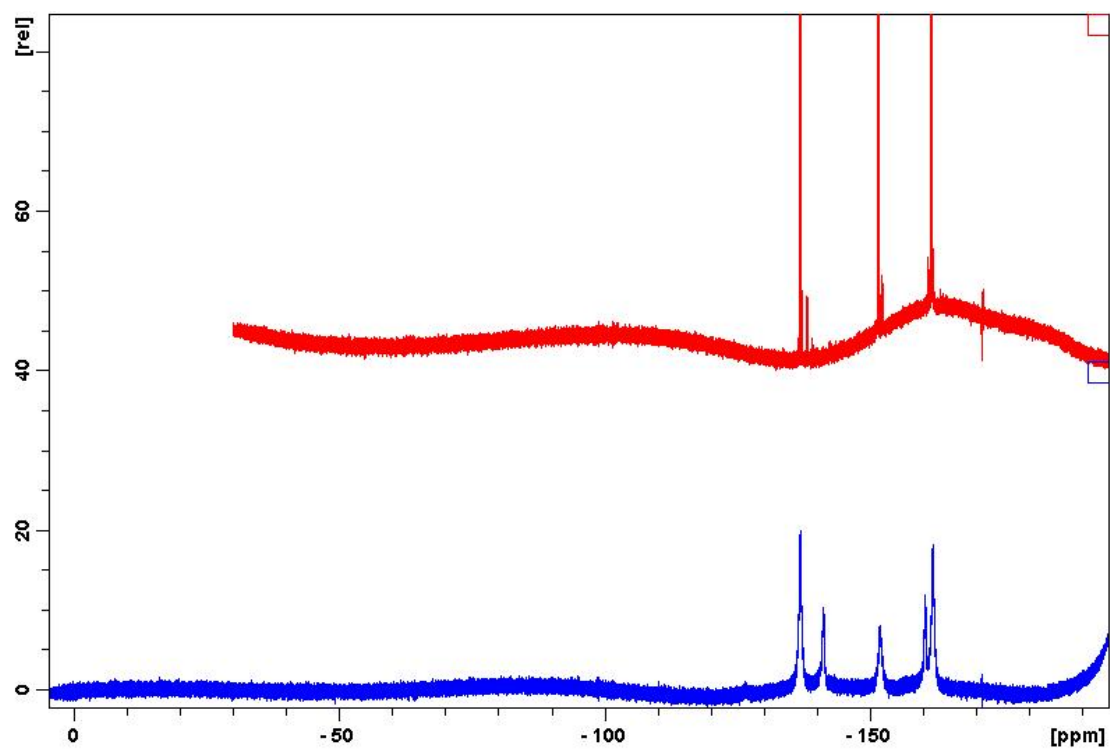
Spectrum 9 and 10: Reaction in NMR tube at 80 °C between resin **31** and KI. Note the formation of CH₂I peak at 3.6 ppm.



Spectrum 11: Hydrolysis product **53** from imidazolidinon synthesis with base (1.25 equiv (table 25, entry 3)).



Spectrum 12: Hydrolysis product from imidazolidinon synthesis with iodide (Table 25, entry 4)



Spectrum 13 A comparison between ^{19}F NMR of resin **68** and the starting material *meso*-tetra(pentafluorophenyl)porphyrin. Note the two new peaks from the phenyl group attached to resin through an amino function.

Appendix B

Publications

Some of the work presented in this thesis has been published as an article in *Synthesis* Fall 2005:

Gram-Scale Synthesis of *N*-Aryl- and *N*-Aryl-*N'*-methyl-piperazines on a Novel, Water-Swellable, Oxethane-Linked Poly(ethylene glycol) High-Loading Resin.
Hans Christian Rudbeck, Ib Johannsen, Ole Nielsen, Thomas Ruhland, Michael Bech Sommer, David Tanner and Robert Dancer, *Synthesis*, **2005**, 3456-62.

Another paper, concerning the scaling-up on resin and reuse is currently in preparation and will be submitted to *Organic Process research and Development* as soon as possible.